

Are Cognitive Processing Problems associated with Hereditary Haemochromatosis?

Gayle McElwee (BA Hons)

*A report submitted in partial requirement for the degree of
Master of Psychology (Clinical) at the University of Tasmania*

I declare that this thesis is my own work and that, to the best of my knowledge and belief, does not contain material from unpublished sources without proper acknowledgement, nor does it contain material which has been accepted for the award of any other higher degree or graduate diploma in any university.

G. McElwee

Gayle McElwee
April 2005

Acknowledgements

Thank you to my supervisors Lisa Gilroy, Clive Skilbeck and Iain Montgomery for coming up with the project after a slight hiccup with the last one... and for their support, advice, proofreading and help with statistics. Thanks to Caroline Ball from the Ambulatory Ward at the Royal Hobart Hospital, Nicki Stevens from the Menzies Centre and Joan Montgomery from the Tasmanian Haemochromatosis Support Group for helping me to recruit participants, and to the staff in Dept. of Psychiatry at the RHH for providing me with a testing space and facilities.

Thanks to the library staff at Document Delivery – Morris Miller Library for fielding about 100 requests while reassuring me not to feel guilty. Thanks to my fiancée Shaun and my parents for all the support, housework and listening, and to the participants who put their dignity on the line to complete a very hard bunch of tests in the name of research.

Contents

Literature Review

Abstract	1
Introduction	2
Haemochromatosis: An Overview	2
<i>Description and diagnostic features</i>	2
<i>The C282Y mutation</i>	3
<i>Importance of early diagnosis and treatment</i>	4
<i>Iron and the body</i>	4
<i>Iron absorption and haemochromatosis</i>	5
Iron and the Brain	7
<i>Importance of iron in brain function</i>	7
<i>Iron transport and the brain</i>	7
<i>Regional brain iron</i>	9
<i>Iron efflux from the brain</i>	10
<i>Evidence for increased brain iron in haemochromatosis</i>	11
<i>Iron and neurodegenerative diseases</i>	12
<i>Iron and Alzheimer's Disease</i>	13
Cognitive Functions that may be impaired	15
<i>Cognitive problems resulting from iron overload</i>	15
<i>Information processing and attention</i>	15
<i>Memory and learning</i>	17
<i>Other factors affecting cognitive processes</i>	18
<i>Pain</i>	19
<i>Fatigue</i>	20
<i>Depression</i>	21
<i>Anxiety</i>	23
<i>Haemochromatosis and Cognitive Functioning – Evidence from</i>	
<i>Case Studies</i>	24
<i>Conclusions and Suggestions for Further Research</i>	25

Empirical Study

Abstract	37
Introduction	38
Method	46
<i>Participants</i>	46
<i>Materials</i>	47
<i>Procedure</i>	52
<i>Design and Data Analysis</i>	53
Results	54
<i>Self-report measures</i>	54
<i>Relationship between self-report and cognitive measures</i>	56
<i>Cognitive Measures</i>	56
Discussion	58
References	68

Abstract

Haemochromatosis is an inherited disease in which the body absorbs iron at an accelerated rate, leading to iron overload and oxidative damage. This occurs in major organs such as the liver, heart and pancreas but may also occur in the brain. The brain has a high iron requirement and few antioxidants compared to the rest of the body, making it particularly vulnerable to oxidative stress. Brain iron overload has been implicated in the pathogenesis and progression of diseases such as Multiple Sclerosis, Parkinson's Disease and Alzheimer's Disease. Case studies have investigated patients who have both haemochromatosis and altered cognitive functioning, although most have involved patients with advanced disease and additional complications, making it difficult to establish causation. If iron-mediated damage occurs within the brain in people with haemochromatosis then it is possible that processes such as memory, learning, attention and information processing speed are affected. These processes are sensitive to brain damage and are commonly influenced by concussion and metabolic disorders. Separating the primary effects of iron overload from secondary effects such as anxiety, depression, fatigue and pain is difficult as each impacts on cognition. Many people with haemochromatosis have complained of cognitive problems. However medical staff have attributed these problems to secondary effects of the disease. No study to date has attempted to investigate the primary effects of haemochromatosis on cognitive functioning using comprehensive neuropsychological tests and a large patient sample with matched controls.

Introduction

Many people with haemochromatosis report cognitive problems, particularly problems with memory, as a symptom of their disease. While these complaints have often been dismissed by health professionals as resulting from fatigue or depression, there is evidence that iron-mediated damage within the brain may be responsible. This paper aims to explore that possibility beginning with describing hereditary haemochromatosis, the roles of iron within the body and the processes by which iron is absorbed and distributed. The alterations in iron absorption and distribution that occur in haemochromatosis are outlined, as well as connections between excess iron and pathology such as Alzheimer's Disease. The cognitive processes that may be affected by iron-mediated damage – attention, processing speed, learning and memory - are outlined. The difficulties in measuring these processes in people who experience other symptoms that are known to affect cognition such as fatigue, pain, depression and anxiety are also discussed.

Haemochromatosis: An Overview

Description and Diagnostic Features

Hereditary haemochromatosis is an autosomal recessive disease in which dietary iron is absorbed at 2-3 times the normal rate. Because iron is not readily excreted, except through blood loss (Pietrangelo, 2003), this excess iron accumulates in major organs, leading to oxidative damage and cell death. The pattern of damage varies from person to person but the liver, heart, brain, pancreas and joints are commonly affected.

The initial symptoms of haemochromatosis are often vague such as a general feeling of illness or fatigue. Subsequent symptoms are specific to organ damage and include arthritis, abdominal pain, weight loss or weight gain, heart arrhythmia, elevated blood sugar levels, bronzed skin, liver problems, impotence and hypothyroidism (Milder, Cook, Stray & Finch, 1980). Secondary effects of iron overload include depression, fatigue, diabetes, heart disease, cirrhosis of the liver, cancer, infertility and neurological problems (Powell, George, McDonnell & Kowdley, 1998).

Hereditary haemochromatosis is caused by a mutation in the HFE gene but diagnosis also depends on the expression of clinical symptoms (Pietrangelo, 2003). Factors such as diet, gender, age, alcohol intake and co-morbid health problems mediate disease expression. While it is currently impossible to predict who will develop symptoms and when (Pietrangelo, 2004), the majority (70%) of people with hereditary haemochromatosis will develop symptoms of iron overload in the third to fifth decade of life (Fletcher & Halliday, 2002). Men generally develop symptoms earlier than women as women are protected from iron overload by menstruation and pregnancy.

The C282Y mutation

The HFE mutation, named C282Y, is thought to have occurred approximately 2000 years ago but was discovered in 1996 by Feder and his colleagues (Rankin, Baxter, Valentine & Powell, 2001; Wood, 2002). The 'recessive' nature of the C282Y mutation means that one gene mutation from each parent must be inherited in order to acquire haemochromatosis (Bassett et al., 1992). Carriers (people with one normal and one mutated HFE gene) often have elevated iron levels but generally do not develop significant health problems. Prevalence rates for the C282Y mutation in

Australia are estimated to be 3.6 per 1000 and 12% of Australians are estimated to be carriers (Bassett et al., 1992).

Importance of early diagnosis and treatment

Early diagnosis of haemochromatosis is essential to promote both quality of life and longevity. The non-specific nature of symptoms and their association with many other diseases makes diagnosis based on symptoms alone extremely difficult (Bomford, 2002). Early diagnosis depends on routine iron-level testing and genetic testing of family members (Brandhagen et al., 2002).

The recommended treatment for haemochromatosis is regular venesection – the removal of approximately 500ml of blood - to stabilise iron levels (Bassett et al., 1992). Treatment can prevent and/or alleviate symptoms of iron overload. Without treatment, organ damage continues and symptoms worsen (Bassett et al., 1992).

Venesection is *not* recommended in the few situations where losing blood would impact on other health problems. In these cases an iron-chelating drug, Deferoxamine, may be used (Emerit, Beaumont & Trivin, 2001).

Iron and the Body

Iron is an essential nutrient for almost all living organisms. It has the ability to readily accept or donate electrons, making it integral to the transportation of oxygen around the body. However, the potentially reactive nature of iron means that it can

“...damage tissue by catalysing the conversion of hydrogen peroxide into free-radical ions that attack cellular membranes, protein and DNA.” (Emerit et al., 2001, p. 333).

To prevent the formation of free radicals, iron levels are carefully regulated (Emerit et

al., 2001). Transferrin and ferritin are iron-binding proteins that transport and store iron safely. Iron regulatory proteins bind to transferrin and ferritin and act to inhibit or facilitate their actions according to the body's needs. Knowledge of how these work, and whether other iron regulatory proteins, transporter proteins or iron sensory elements exist is yet unknown (Lieu, Heiskala, Peterson & Yang, 2001).

The body's main source of iron is recycled iron (Pietrangelo, 2003) - iron is transported within the bloodstream to bone marrow where erythrocytes (red blood cells) are produced. When these are destroyed they are consumed by reticuloendothelial cells, which release iron back into the bloodstream.

Body iron levels are controlled through regulating the uptake of dietary iron (Pietrangelo, 2003). Crypt cells in the intestine receive information regarding current iron stores and needs. As they mature into absorptive enterocytes, they regulate iron uptake by expressing more or less iron-transport receptors on their surface (Fleming & Sly, 2002).

Iron absorption and haemochromatosis

How the HFE mutation leads to increased absorption of dietary iron is not fully understood. Most of the knowledge in this area is derived from studies of cultured cells and from genetically modified mice (Fleming & Sly, 2002). In healthy people the HFE protein associates with transferrin receptors (Fleming & Sly, 2002) and both are expressed on the surface of cells (Pietrangelo, 2003). This combination is thought to play a major role in iron uptake, particularly in enterocytes (Fleming & Sly, 2002). The transferrin/iron/HFE complex is internalised by the cell and separated

in the endosome. Transferrin is recycled to the cell's surface and iron is used immediately or stored as ferritin; the fate of HFE at this stage is unknown (Fleming & Sly, 2002).

The C282Y mutation results in inadequate HFE expression on the cell's surface and hence a reduction in transferrin-mediated iron uptake, leading to iron deprivation within the cell. Future crypt cells are then programmed to absorb more iron to correct this deficit (Fleming & Sly, 2002). The new crypts absorb iron through non-transferrin pathways such as divalent metal transport 1 protein (DMT1). As their internal iron levels increase, they export more iron into the bloodstream (Fleming & Sly, 2002). Reticuloendothelial cells are also reported to up-regulate their iron intake and release more iron into the bloodstream (Pietrangelo, 2004).

Hepcidin, a liver peptide, has recently been implicated in iron overload in haemochromatosis (Limdi & Crampton, 2004). Hepcidin is thought to relay information about body iron stores to both enterocytes and reticuloendothelial cells via the HFE/transferrin pathway and is particularly important in *reducing* iron uptake. The expression of hepcidin is significantly decreased in mice that are HFE deficient (Pietrangelo, 2004).

While this is only one hypothesis of how iron absorption is modified in haemochromatosis, it is the one most supported by current evidence. More studies are required to confirm these findings (Fleming & Sly, 2002).

Iron and the Brain

Importance of iron in brain function

It was once thought that iron did not cross the blood brain barrier (BBB) and therefore could not affect brain functioning in people with hemochromatosis (Sachdev, 1993).

It is now known that iron does cross the BBB and it is likely that there is a dynamic exchange of iron between organs, including the brain. This system allows iron to be quickly transferred from other organs to the brain when iron levels are low (Connor, Menzies, Joseph, Burdo & Boyer, 2001a).

Within the brain, iron is involved in "...oxygen transport, electron transport, glucose metabolism, and the synthesis of neurotransmitters, myelin, and DNA replication..." (Pinero & Connor, 2000, p. 435). Areas of the brain that are rich in iron are also rich in dopamine, GABA and serotonin receptors and when iron levels are low there is a decrease in both GABA, glutamate, and dopamine receptor expression (Sachdev, 1993). The brain has a high iron requirement (Pinero & Connor, 2000) and iron deficiency causes cell loss and decreased function within the brain, with significant and long-lasting effects on learning and cognitive and motor functioning in both children and adults (Burdo & Connor, 2002).

Iron Transport and the Brain

The blood-brain barrier poses specific challenges to the transportation of iron to and from the brain. The various regions, functions and cell types that exist within the brain, in addition to changing developmental iron needs, also complicate iron homeostasis (Connor et al., 2001a).

Iron uptake within the brain is mediated by transferrin receptor expression.

Transferrin receptors have been found on the BBB (Connor et al., 2001a) and some studies have found that the iron-transferrin complex is transported across the BBB.

However, more iron than transferrin crosses the BBB, indicating that additional transport mechanisms are involved (Connor et al., 2001a). DMT1 is thought to be involved in iron transportation to the brain. Belgrade rats, which have a defect in DMT1, have very low brain iron levels (Connor et al., 2001a). In humans, DMT1 occurs in neurons within the striatum, thalamus, choroid plexus and the cerebellum (Pinero & Connor, 2000). DMT1 has also been found in the blood vessels that line the brain, the choroid plexus and cells lining the brain/ventricle interface (Connor et al., 2001a).

A third iron-transport protein, lactoferrin, also occurs in the brain. Lactoferrin is part of the transferrin family but has a greater binding capacity than transferrin (Thompson, Shoham & Connor, 2001). Occurring in milk, mucosal tissues and leukocytes (Powell & Halliday, 1985), it has also been found in neurons, brain vasculature (Thompson et al., 2001) and the substantia nigra (Connor et al., 2001a). Its expression is increased in patients with Parkinson's Disease (Burdo & Connor, 2002; Pinero & Connor, 2000) in association with increased intraneuronal iron levels and degeneration of dopaminergic neurons within the substantia nigra.

Iron is also transported to areas of the brain outside the BBB such as the posterior pituitary and median eminence. Tanycytes, glial cells that line the ventricles, are thought to play a role in transporting iron to these areas (Connor et al., 2001a) as these

cells surround the circumventricular areas and stain heavily for iron and ferritin (Pinero & Connor, 2000).

Iron is distributed within the brain via cerebrospinal fluid (CSF). The choroid plexus manufactures transferrin and releases iron-laden transferrin into CSF (Connor et al., 2001a). Transferrin saturation levels within CSF vary but have been reported at full capacity. Other iron transport systems within CSF include proteins such as citrate, adenosine triphosphate (Cheepsunthorn, Palmer, Menzies, Roberts & Connor, 2001), ascorbate and ferritin (Burdo & Connor, 2002).

Iron recycling also occurs in the brain. Microglia obtain iron through phagocytosis and release iron to oligodendrocytes for myelin production. Oligodendrocytes also sequester excess iron to microglia, which can be regained if brain damage occurs (Connor et al., 2001a).

Regional Brain Iron

Iron levels are highest in areas of the brain that are associated with motor functions such as the motor cortex, basal ganglia and other subcortical structures (Connor et al., 2001a). These areas are involved in translating cognitions into actions, initiating and maintaining movement, developing habits and skills and procedural memory (Lezak, Howieson & Loring, 2004). The substantia nigra and the globus pallidus have high iron levels but low transferrin densities (Pinero & Connor, 2000; Sachdev, 1993) and are connected to the nucleus accumbens and the caudate putamen, which have low iron levels and high transferrin receptor densities. It is thought that the areas abundant in transferrin receptors deliver iron to areas that have few transferrin receptors.

White matter, which transmits neural impulses within and between cortical and subcortical areas (Lezak et al., 2004), has the highest concentration of iron in the brain. Oligodendrocytes require large amounts of iron for the production and maintenance of myelin (Pinero & Connor, 2000), which enhances conduction speed. Oligodendrocytes rely primarily on ferritin for their iron requirements (Burdo & Connor, 2002). While oligodendrocytes are most prevalent in white matter, they also occur in the substantia nigra and striatum (Connor et al., 2001a).

Ferritin plays an important role within the brain as an iron storage system. Ferritin has a high iron-binding capacity and sequesters excess iron during traumatic events such as hypoxia and seizures. H-type ferritin is a fast-acting system, able to sequester and release iron quickly, whereas L-ferritin is a slower-acting, longer-term storage system (Cheepsunthorn et al., 2001). Ferritin is found mainly within white matter and the cortex (Pinero & Connor, 2000).

Iron Efflux from the Brain

Inadequate efflux may be responsible for some types of iron-mediated damage within the brain (Connor et al., 2001a). Little is known about how brain iron efflux occurs (Burdo & Connor, 2002; Connor et al., 2001a), however it has been demonstrated that iron can be transported across the ventricle lining into the bloodstream (Burdo & Connor, 2002). Ceruloplasmin is an endogenous iron cheater that may facilitate iron efflux from the brain (Thompson et al., 2001). In animals, iron efflux occurs in a regionally specific pattern that changes according to developmental stage. If

inadequate iron efflux is the cause of iron overload, some areas may be more susceptible to damage than others (Connor et al., 2001a).

Evidence for Increased Brain Iron in Haemochromatosis

In the 1930's and 1940's, brain iron levels were investigated post-mortem in people with haemochromatosis. Iron levels were not found to be elevated in areas that were protected by the BBB (Sachdev, 1983). However, techniques have become more sophisticated over time and recent results from MRI, CT and transcranial sonography have suggested that brain iron levels can be abnormally high in people with haemochromatosis, particularly within the basal ganglia (Burdo & Connor, 2002; Connor et al., 2001a; Pinero & Connor, 2000).

The HFE protein has been found to associate with transferrin receptors in the choroid plexus, brain capillaries and ependymal cells. The aforementioned increase in iron uptake that occurs in the intestine due to the HFE mutation may also occur in the brain (Connor et al., 2001b). Areas of the brain that are highest in transferrin receptors include the cortex, amygdala, hippocampus and the brainstem (Pinero & Connor, 2000) which are broadly involved in awareness and behaviour, emotional processing, attention and learning, memory, and consciousness and arousal, respectively (Lezak, 1995). An experiment with HFE-gene modified mice found significantly elevated brain iron levels at 20 weeks of age compared to controls (Connor et al., 2001a). These findings indicate that iron accumulates at an accelerated rate in the brains of mice with haemochromatosis. It is unknown whether these findings generalise to humans.

Iron and neurodegenerative diseases

The brain naturally has high iron levels (Connor et al., 2001b; Pinero & Connor, 2000) and few antioxidants compared to the rest of the body, making it particularly vulnerable to oxidative damage (Connor, Snyder, Arosio, Loeffler, & DeWitt, 1995; Thompson et al., 2001). Iron overload and oxidative damage has been implicated in the pathogenesis and progression of many neurodegenerative diseases, particularly movement disorders, and iron overload is prominent in areas of the brain associated with motor control (Burdo & Connor, 2002). Below is a brief summary:

Disease

Studies/Reviews

Fredreich's ataxia

Symptoms: Ataxia, motor weakness,
proprioceptive loss, dysarthria
Increased iron in: Dentate nucleus
& mitochondria

Burdo & Connor, 2002
Connor et al., 2001a
Pinero & Connor, 2000
Lieu et al., 2001
Thompson et al., 2001

Parkinson's Disease

Symptoms: Rigidity, tremor, bradykinesia
death of dopaminergic neurons
Increased iron in: Substantia Nigra,
striatum, Lewy bodies

Burdo & Connor, 2002
Connor et al., 2001a
Connor et al., 1995
Gerlach, Ben-Schadar
Riederer & Youdim, 1994
Lieu et al., 2001
Pinero & Connor, 2000
Sachdev, 1993
Thompson et al., 2001

<i>Multiple Sclerosis</i>	Burdo & Connor, 2002
Symptoms: Fatigue, weakness, dysarthria, sensory changes	Connor et al., 2001a Pinero & Connor, 2000
Increased iron in: Oligodendrocytes	Thompson et al., 2001
<i>Huntington's Disease</i>	Burdo & Connor, 2002
Symptoms: Cognitive, motor and psychiatric disturbance	Connor et al., 2001a Gerlach et al., 1994
Increased iron in: Striatum	Pinero & Connor, 2000
<i>Hallervorden-Spatz Syndrome</i>	Burdo & Connor, 2002
Symptoms: Extra pyramidal dysfunction rigidity, dystonia, choreoathetosis	Connor et al., 2001a Jones & Hedley-Whyte, 1983
Increased iron in: Substantia Nigra, globus pallidus	Lieu et al., 2001 Pinero & Connor, 2000 Thompson et al., 2001

The role of iron in Alzheimer's Disease will be explored in more detail, as it is most relevant to this study.

Iron and Alzheimer's Disease

Alzheimer's Disease (AD) is characterised by a progressive deterioration in memory, personality and intellectual ability. This is associated with neuronal death and the formation of amyloid plaques and neurofibrillary tangles in cortical and sub-cortical areas (Gerlach et al., 1994). Excess iron within the brain is a consistent finding in people with AD (Connor et al., 2001b) and it is hypothesised that iron overload may be a risk factor for AD (Connor et al., 2001a).

In AD, iron levels are reportedly increased in the hippocampus, prefrontal cortex, amygdala, frontal lobes, inferior parietal lobes, temporal cortex, nucleus basalis, globus pallidus and the motor cortex. Iron levels are *decreased* in the occipital cortex and substantia nigra (Pinero & Connor, 2000; Sachdev, 1993). Elevated iron levels are present in the basal ganglia at the point of onset of AD and therefore iron accumulation is thought to play a role in the pathogenesis of the disease (Burdo & Connor, 2002; Lieu et al., 2001).

Increased iron is associated with neuritic plaques that are the hallmark of AD (Connor et al., 2001a; Connor et al., 2001b). Changes in iron homeostasis are thought to influence the production of amyloid – the key component of the plaques (Burdo & Connor, 2002; Thompson et al., 2001) - and increased iron promotes the deposition of plaques in vitro (Connor et al., 2001b). Iron is also found in neurons that contain neurofibrillary tangles (Pinero & Connor, 2000) and may play a role in their formation (Thompson et al., 2001).

Iron regulatory proteins maintain iron homeostasis within the brain by controlling the expression of transferrin and ferritin. Iron Regulatory Protein 2 (IRP2) is found in intraneuronal lesions, senile plaques and neurofibrillary tangles (Lieu et al., 2001) and its expression is altered in AD (Pinero & Connor, 2000). This alteration leads to an up-regulation of transferrin receptors and a down-regulation of ferritin, resulting in cells increasing their iron uptake without the capacity to store it safely. Iron accumulates faster than ferritin production in regions of the brain that have the highest rates of degeneration in people with AD, whereas areas that have equal ferritin-iron levels are relatively spared (Burdo & Connor, 2002). In healthy brains, ferritin levels

increase linearly with iron levels and sequester excess iron to protect cells (Lieu et al., 2001; Pinero & Connor, 2000).

Treatments for AD have included iron-chelating drugs such as deferoxamine. These have been successful in reducing iron levels and slowing progression of AD (Pinero & Connor, 2000; Sachdev, 1993). The administration of anti-oxidants such as vitamin E, oestrogen and selegiline also delay the onset of AD (Connor et al., 2001b; Sano, 2003), providing further evidence that iron-induced oxidative damage contributes to the pathology of AD.

Cognitive Functions that may be Impaired

Cognitive Problems Resulting from Iron Overload

Because iron crosses the BBB and excess iron can accumulate in the brain, cognitive processes are likely to be affected in people with haemochromatosis. Those that are most sensitive to brain damage include memory, learning, information processing speed and attention. These functions are frequently impaired by diffuse brain damage such as concussion and metabolic disorders (Lezak et al., 2004). While all of these functions are "...inextricably bound together – different facets of the same thing." (Lezak et al., 2004, p. 20), they will be described separately.

Information Processing and Attention

Information processing speed is the rate at which the nervous system can convey messages (Gronwall & Sampson, 1974). Reduced information processing speed affects many other areas of cognition including attention, learning and memory

(Felmingham, Baguley & Green, 2004). The mechanisms underlying information processing speed are not known, although diffuse brain damage is frequently the cause of processing speed deficits (Felmingham et al, 2004; Gronwall & Sampson, 1974). Descriptions of information processing often underlie or overlap with descriptions of attention (van Zomeren & Spikman, 2003; Vlaar & Wade, 2003).

There are many definitions of attention. It is a resource that filters incoming information, selects certain inputs for processing, and processes information (Eccleston & Crombez, 1999). It can be conceptualised as a cognitive spotlight that can be directed at something to focus on it in more detail. Its scope can be widened but this causes its brightness to be diminished, as its overall capacity is limited (Lieberman, 2004).

Attentional tasks are those that require planning, decision making, learning new sequences, responding to new or dangerous stimuli, or overcoming a habitual activity or response (Norman & Shallice, 1986). Many operations can be performed automatically with limited attentional control (Eccleston, 1994). Attention has many facets - divided attention, sustained attention, selective attention and focused attention - and while these can never be completely separated from each other, tests of attention generally focus one of these aspects (Rogers, 2000; van Zomeren & Spikman, 2003).

Deficits in attention and information processing affect other cognitive processes such as memory and learning because information must be attended to and processed before it can be retained. The most sensitive tests of attention and information processing deficits are speed-based tests. The Stroop colour word task, Paced

Auditory Serial Addition Test (PASAT), Information Processing Task A and choice reaction time tasks are all speed-based and measure various aspects of attention and information processing speed.

Memory and Learning

Learning is defined as the ability to acquire knowledge, while memory is the ability to retain it (Lieberman, 2004). However the two processes are dependent on each other and at times difficult to separate so they will be considered together.

Memory consists of encoding (recording an experience by making an internal representation of it), storage (holding that experience over time), and retrieval (when the remembered information is used in some way) (Lieberman, 2004). A number of models of memory have been proposed and only a few will be discussed. The Atkinson-Shiffrin model includes three separate memory systems that work together: sensory memory stores a vast amount of information in a buffer of very short-term capacity and transfers a small amount of this into short-term memory. Short-term memory holds approximately seven pieces of information for around 30 seconds. Some of this information is then transferred to long-term memory, which holds an infinite amount of information for a seemingly unlimited time (Lieberman, 2004).

The concept of short-term memory was further developed by Baddeley (1986) who proposed that it is more than just a storage system. Baddeley and Hitch devised a model of 'working memory' that consists of a central executive control centre and two slave systems: an articulatory loop specialised for processing language, and a visual-spatial sketchpad for retention of visual and spatial material (Baddeley, 1986).

The visual-spatial component has since been divided into separate visual and spatial systems (Della Salla, Gray, Baddeley, Allamano & Wilson, 1999). The central executive is able to process information from many sources, possesses attentional resources and can select and operate different control processes to aid problem solving and decision-making (Baddeley, 1986). The central executive is the least investigated aspect of working memory and, as such, little is known about its functions (Lieberman, 2004).

Tasks that are frequently used to measure memory include recalling previously presented word lists, complex designs, pictures, numbers or stories. Tests of working memory involve maintaining a number of items in short term memory while performing concurrent processes such as counting or problem solving (Gavens & Barrouillet, 2004). The more demanding the processing component (ie the more attentional resources required), the less information is remembered.

Forgetting can be attributed to losing previously attained information. However, it may be more likely that the information is just difficult to retrieve. When cues are given regarding the 'forgotten' information, recall is enhanced. Recognition tasks, where cues are given regarding previously presented information, elicit greater amounts of information than recall tasks, where no cues are given (Lieberman, 2004).

Other factors affecting cognitive processes

Cognitive processing is affected by factors other than organic damage. Anxiety, depression, fatigue and pain can all adversely impact on cognition and are common

outcomes of brain injury and disease (Lezak et al., 2004). Depression and fatigue are particularly common symptoms of haemochromatosis (Sachdev, 1993).

Pain

Many studies have investigated the effects of cognition on pain, however few studies have focused on the effects of pain on cognition (Grigsby, Rosenberg & Busenbark, 1995). The complex nature of pain makes measurement and interpretation difficult as secondary changes in mood, sleep and lifestyle mediate the effects of pain on cognition (Ziegler & Paolo, 1995).

For example, Grace, Nielson, Hopkins & Berg (1999) found that fibromyalgia patients performed more poorly than matched controls on the PASAT and measures from the Wechsler Memory Scale – Revised, however, cognition was more related to sleep quality and anxiety levels than to pain intensity. Iezzi, Duckworth, Vuong, Archibald and Klinck (2004), using a regression analysis, found that pain severity was a significant predictor of memory scores as measured by the Wechsler Memory Scale-Revised, independent of its secondary effects. However, in this study secondary effects were measured only by the SCL-90. Bell, Primeau, Sweet and Lofland (1999) found no negative effects of pain on cognition, although these results were based on comparisons with test norms rather than a matched control group. Overall, most studies have found that participants with severe pain demonstrate impairments on measures of attentional capacity, processing speed and psychomotor speed (Hart Martelli & Zasler, 2000, Martelli, Grayson & Zasler, 1999) although non-clinical pain has little effect on cognitive functioning (Hart et al., 2000, Ziegler & Paolo, 1995).

Pain is a powerful stimulus and indicates danger (Grigsby et al., 1995). It therefore interrupts other cognitive activities and is difficult to disengage from (Eccleston & Crombez, 1999). Apkarian, Sosa and Krauss et al. (2004) proposed that chronic pain impacts on other cognitive processes because it competes successfully for cognitive resources.

The findings from studies of clinical pain may not generalise to patients with haemochromatosis. It is unlikely that the majority of people with haemochromatosis would experience pain that is severe enough to impact on cognitive functioning. However, the secondary changes in mood and lifestyle associated with chronic pain that influence cognitive functioning may affect people with haemochromatosis.

Fatigue

Few studies have investigated the impact of fatigue on cognitive functioning (Short, McCabe & Tooley, 2002). The majority of research has focused on cognitive functioning in patients with Chronic Fatigue Syndrome (CFS) (Dobbs, Dobbs & Kiss, 2001).

Studies of CFS patients have yielded conflicting results. Some have found deficits in information processing speed (Bushio, Tiersky, Deluca & Natelson, 2004; Deluca, et al., 2004), attention and motor speed (Bushio et al., 2004) compared to matched controls, with negative findings on tests of memory and executive functioning. Other studies have found significant deficits in learning, memory (Marcel, Komaroff, Fagioli, Kornish & Albert, 1996) and executive functioning (Dobbs et al., 2001) compared to matched controls, with no between-group differences in attention

(Marcel et al., 1996). The most consistently documented cognitive deficits in review papers include complex information processing efficiency and speed (Michiels & Cluydts, 2001; Tiersky, Johnson, Lange, Natelson & DeLuca, 1997) and working memory and learning (Michiels & Cluydts, 2001).

Using individual rather than group comparisons, Vercoulen, Bazelmas, Swanink, Galama and Fennis (1998) found that only a subgroup (approximately 30%) of patients with CFS demonstrated impairments in cognitive functioning, with the majority performing within the average range. This may explain the discrepant findings between studies. Although patients with CFS tend to express high levels of psychological distress, this does not seem to fully account for their performance on cognitive tests (Crowe & Casey, 1999; Daly, Komaroff, Bloomingdale, Wilson & Albert, 2001; Kane, Gants & DiPino, 1997; Marcel et al., 1996; Short et al., 2002; Vercoulen et al., 1998).

The results from studies of CFS may not generalise to other diseases such as haemochromatosis as factors other than fatigue may account for differences in cognitive functioning. The heterogeneity of CFS even makes comparisons between populations from different studies and generalisations to the wider CFS population difficult.

Depression

Depression frequently co-occurs with chronic diseases such as haemochromatosis. It is widely accepted that cognitive deficits occur in people with major depression

(Naismith et al., 2003; Veiel, 1997) although studies of different cognitive processes have yielded mixed results (Airaksinen, Larsson, Lundberg & Forsell, 2004).

Veiel (1997) conducted a meta-analysis of methodologically sound studies comparing younger adults (aged from 20's to 50's) meeting DSM III criteria for major depression to matched controls on a variety of cognitive measures.

The majority of studies found no significant differences between depressed samples and controls on measures of attention and concentration, as assessed primarily by digit span or block span tasks (Veiel, 1997). A small proportion of depressed individuals (11%) scored within the defective range on tests of verbal fluency, primarily measured by the Controlled Oral Word Association Test. Measures of visual and spatial functions - such as the Complex Figure Test, Block Design and Object Assembly - and measures of non-verbal learning for visually presented material indicated that approximately 15% of depressed patients experienced difficulties compared to controls. Tests of verbal learning and memory yielded similar results with 14-15% of depressed patients scoring within the defective range on tests of paired associations, list learning and story recall (Veiel, 1997).

The most prominent effects of depression on cognitive functioning were noted on tests of 'mental flexibility and control' which are sensitive to brain dysfunction. A total of 50% of depressed participants scored within the defective range on these tasks. Reaction times were also impaired (Veiel, 1997).

Elderkin-Thompson, Kumar, Bilker, et al. (2003) and Airaksinen et al. (2004) assessed the impact of depression severity on cognitive processing in older and younger population samples, respectively. Participants with major depression tended to perform more poorly than participants with minor depression, with healthy controls eliciting the highest scores on measures of verbal skills and maintenance of set (Elderkin-Thompson et al., 2003). Episodic memory scores differentiated the major in Airaksinen et al.'s study.

Weiland-Feidler et al. (2004) found that depression has long-lasting effects on sustained attention, even when the depressive episode has ceased. However visual and verbal memory, learning and attention set-shifting appear to be state-dependent.

Rohling, Green, Allen and Iverson (2002) investigated the relationship between self-reported depression and cognitive functioning, and found no significant relationship between reported symptoms and actual deficits on a wide range of cognitive tests. Rohling et al. also expected participants with higher levels of depression to perform more poorly on tests that required more mental effort (as opposed to automatic processing). Again, no significant relationship was found between the amount of effort required and performance deficits. Rohling et al. (2002) had excluded patients who failed symptom validity tests, and concluded that this may be why their findings differed from the studies that they aimed to replicate – none of their patients were ‘faking bad’, which may be the case in other studies using depressed samples.

Anxiety

The effect of anxiety on cognitive functioning is thought to be an inverted U function where excessively low or high anxiety impairs performance (Gladsjo et al., 1998).

Anxiety is associated with increased vigilance, surveillance and evaluation of the environment for signs of danger. It engages attention and competes with other cognitive tasks for resources (Nitschke, Heller & Miller, 2000). Anxiety in the form of worry is thought to utilise the central executive and the articulatory loop and therefore decrease the efficiency of performing other cognitive tasks that utilise these resources (Eysenck & Calvo, 1992).

There are some studies that have assessed the effects of non-clinical anxiety on neuropsychological functioning (Lezak et al., 2004) although most have focused on specific anxiety disorders (Airaksinen, Larsson & Forsell, 2005). While clinical anxiety is often detrimental to cognitive functioning (Waldstein, Ryan, Jennings, Muldoon & Manuck, 1997), studies of non-clinical anxiety have provided largely non-significant findings on tests of verbal short term memory and learning (Kizilbash, Vanderploeg & Curtiss, 2002), executive functioning, processing speed, verbal fluency (Temple, Horner & Taylor, 2004), verbal long term memory and attentional capacity (Waldstein et al., 1997).

Haemochromatosis and Cognitive Functioning – Evidence from Case Studies

Case studies have investigated patients with haemochromatosis and altered cognitive functioning, although most have involved patients with advanced disease and additional complications. Victor, Adams and Cole (1965) collected medical data on patients with hepatic coma, a common outcome of untreated haemochromatosis and

Wilson's Disease (Jones & Hedley-Whyte, 1983), and noted anecdotally that many patients demonstrated cognitive impairments. They reported that patients exhibited slowed responses, an incapacity to form ideas or think logically, poor attention span, impaired short-term memory and lack of insight into their deficits. Many presented as apathetic and disinterested, although some were impulsive and agitated. Symptom severity varied between patients – some were clearly disoriented while others' impairments only became evident through psychometric testing.

Victor et al. (1965) administered the WAIS and the WMS to 15 of their 27 patients. Deficits were noted on all tests, both verbal and visual, with severe impairments found for measures of abstract reasoning and retention of new information. Cerebellar damage was evident from gait problems, lurching, clumsiness and frequent falls. Tremor, ataxia, slowed speech and poor volume control were also common (Victor et al., 1965). On investigation, parenchymal damage was evident in the cerebral cortex, white matter, basal ganglia, cerebellar cortex and dentate nucleus. Victor et al. concluded that the observed cognitive problems were secondary to extensive liver damage rather than due to iron or other metals accumulating in the brain.

Jones and Hedley-Whyte (1983) reported two case studies of people with both haemochromatosis and AD. Their patients were treated for haemochromatosis, one with venesection and one with a low protein diet, and symptoms of dementia subsequently improved. Symptoms then worsened when patients' protein limit was increased. Post-mortem examination was performed for one patient and Alzheimer type II astrocytes were found in the cerebral cortex and the cerebellar dentate nucleus.

Astrocytes in the caudate, putamen and dentate nuclei contained iron (Jones & Hedley-Whyte, 1983). No psychometric test scores were reported for these cases.

Conclusions and Suggestions for Further Research

People with haemochromatosis frequently complain of cognitive problems, particularly memory problems. Iron overload and oxidative damage impairs the functioning of various organs such as the liver, heart and pancreas and evidence indicates that this may also occur in the brain. Brain iron overload is noted in diseases such as Hallervorden-Spatz Syndrome, Parkinson's Disease, Huntington's Disease and Alzheimer's Disease and is implicated in their pathogenesis and progression. The hippocampus, basal ganglia and white matter are particularly susceptible to iron-mediated damage and therefore motor functions, memory, learning, information processing speed and attention are likely to be affected.

Mechanisms for iron absorption and transport are still being discovered and additional research is required to elucidate how iron overload occurs within the body, particularly the brain. Brain iron absorption and transport is complicated due to the many different brain regions and changing developmental requirements. It is likely that the brain utilises several methods of iron transportation and distribution.

It appears that no researchers to date have investigated cognitive functioning in haemochromatosis with the exception of case studies. These studies have frequently been confounded by comorbid diseases and alcohol abuse and have failed to consider the impact of mood, fatigue and pain on cognitive functioning. More comprehensive investigations including sensitive neuropsychological tests, exclusion of participants

with possible confounding problems and a large sample of participants with a matched control group are required to clarify whether objective evidence exists for cognitive processing difficulties associated with haemochromatosis.

References

- Airaksinen, E., Larsson, M., Lundberg, L., & Forsell, Y. (2004). Cognitive functions in depressive disorders: evidence from a population-based study. *Psychological Medicine, 34*, 83-91.
- Airaksinen, E., Larsson, M., & Forsell, Y. (2005). Neuropsychological functions in anxiety disorders in population-based samples: Evidence of episodic dysfunction. *Journal of Psychiatric Research, 39*, 207-214.
- Apkarian, A. V., Sosa, Y., Krauss, B. R., Thomas, P. S., Fredrickson, B. E., Levy, R. E., Harden, R. N., & Chialvo, D. R. (2004). Chronic pain patients are impaired on an emotional decision-making task. *Pain, 108*, 129-136.
- Baddeley, A. D. (1986). *Working Memory*. Oxford: Clarendon Press.
- Bassett, M., Reed, W., Powell, L., Halliday, J., Olynk, J., Watson, K., & Smallwood, R. (1992). *Some facts about haemochromatosis (Iron Overload Disease)*. Sydney: Australian Gastroenterology Institute.
- Bell, B. D., Primeau, M., Sweet, J. J., & Lofland, K. R. (1999). Neuropsychological functioning in migraine headache, nonheadache chronic pain, and mild traumatic brain injury patients. *Archives of Clinical Neuropsychology, 14*, 389-399.
- Bomford, A. (2002). Genetics of Haemochromatosis. *The Lancet, 360*, 1673-1681.
- Brandhagen, D., Fairbanks, V., & Baldus, W. (2002). Recognition and management of hereditary hemochromatosis. *American Family Physician, 65*, 853-860.
- Burdo, J. R., & Connor, J. R. (2002). Iron Transport in the central nervous system. In D. M. Templeton (Ed.), *Molecular and Cellular Iron Transport*. (pp. 487-508). New York: Marcel Dekker, Inc.

- Busichio, K., Tiersky, L. A., Deluca, J., & Natelson, B. H. (2004). Neuropsychological deficits in patients with chronic fatigue syndrome. *Journal of International Neuropsychological Society*, 10, 278-285.
- Cheepsunthorn, P., Palmer, C., Menzies, S., Roberts, R. L., & Connor, J. R. (2001). Hypoxic/ischemic insult alters ferritin expression and myelination in neonatal rat brains. *The Journal of Comparative Neurology*, 431, 382-396.
- Connor, J. R., Menzies, S. L., Joseph, R., Burdo, B. A. & Boyer, P. (2001a). Iron and iron management proteins in neurobiology. *Paediatric Neurology*, 25, 118-129.
- Connor, J. R., Milward, S. M., Sampietro, M., Boyer, P., Percy, M. E., Vergani, C., Scott, R. J., & Chorney, M. (2001b). Is hemochromatosis a risk factor for Alzheimer's Disease? *Journal of Alzheimer's Disease*, 3, 471-477.
- Connor, J. R., Snyder, B. S., Arosio, P., Loeffler, D. A., & DeWitt, P. (1995). A quantitative analysis of isoferritins in select regions of aged, Parkinsonian, and Alzheimer's diseased brains. *Journal of Neurochemistry*, 65, 717-724.
- Crowe, S. F. & Casey, A. (1999). A neuropsychological study of the chronic fatigue syndrome: Support for a deficit in memory function independent of depression. *Australian Psychologist*, 34, 70-75.
- Daly, E., Komaroff, A. L., Bloomingdale, K., Wilson, S., & Albert, M. S. (2001). Neuropsychological function in patients with chronic fatigue syndrome, Multiple Sclerosis, and depression. *Applied Neuropsychology*, 8, 12-22.
- Della Salla, S., Gray, C., Baddeley, A., Allamano, N., & Wilson, L. (1999). Pattern span: a tool for unwinding visuo-spatial memory. *Neuropsychologia*, 37, 1189-1199.

- Deluca, J., Christodoulou, C., Diamond, B. J., Rosenstain, E. D., Kramer, N., & Natelson, B. H. (2004). Working memory deficits in chronic fatigue syndrome: Differentiating between speed and accuracy of information processing. *Journal of the International Neuropsychological Society*, 10, 101-109.
- Dobbs, B.M., Dobbs, A. R., & Kiss, I. (2001). Working memory deficits associated with chronic fatigue syndrome. *Journal of the International Neuropsychological Society*, 7, 285-293.
- Eccleston, C. (1994). Chronic pain and attention: A cognitive approach. *British Journal of Clinical Psychology*, 33, 535-547.
- Eccleston, C. & Crombez, G. (1999). Pain demands attention: A cognitive-affective model of the interruptive function of pain. *Psychological Bulletin*, 125, 356-366.
- Elderkin-Thompson, V., Kumar, A., Bilker, W. B., Dunkin, J. J., Mintz, J., Moberg, P. J., Mesholam, R. I., & Gur, R. E. (2003). Neuropsychological deficits among patients with late-onset minor and major depression. *Archives of Clinical Neurology*, 18, 529-549.
- Emerit, J., Beuamont, C., & Trivin, F. (2001). Iron metabolism, free radicals, and oxidative injury. *Biomedical Pharmacotherapy*, 55, 333-339.
- Eysenck, M. W., & Calvo, M. G. (1992). Anxiety and performance: The processing efficiency theory. *Cognition and Emotion*, 6, 409-434.
- Felmingham, K. L., Baguley, I. K., & Green, A. M. (2004). Effects of diffuse axonal injury on speed of information processing following severe traumatic brain injury. *Neuropsychology*, 18, 564-571.

- Fleming, R. E., & Sly, W. S. (2002). Mechanisms of iron accumulation in hereditary hemochromatosis. *Annual Review of Physiology*, 64, 663-680.
- Fletcher, L. M., & Halliday, J. W. (2002). Haemochromatosis: Understanding the mechanism of disease and implications for diagnosis and patient management following the recent cloning of novel genes involved in iron metabolism. *Journal of Internal Medicine*, 251, 181-192.
- Gavens, N., & Barrouillet, P. (2004). Delays of retention, processing efficiency, and attentional resources in working memory span development. *Journal of Memory and Language*, 51, 644-657.
- Gerlach, M., Ben-Schadar, D., Reiderer, P., & Yuodim, B. M. (1994). Altered brain metabolism of iron as a cause of neurodegenerative diseases? *Journal of Neurochemistry*, 63, 793-807.
- Gladysjo, J. A., Rapaport, M. H., McKinney, R., Lucas, J. A., Rabin, A., Oliver, T., Davis, J., Auerbach, M., & Judd, L. L. (1998). A neuropsychological study of panic disorder: Negative findings. *Journal of Affective Disorders*, 49, 123-131.
- Grace, G. M., Nielson, W. R., Hopkins, M., & Berg, M. A. (1999). Concentration and memory deficits in patients with fibromyalgia syndrome. *Journal of Clinical and Experimental Neuropsychology*, 21, 477-487.
- Grigsby, J., Rosenberg, N. L., & Busenbark, D. (1995). Chronic pain is associated with deficits in information processing. *Perceptual and Motor Skills*, 81, 403-410.
- Gronwall, D. M. A., & Sampson, H. (1974). *The Psychological Effects Of Concussion*. New Zealand: Auckland Univeristy Press/Oxford University Press.

- Hart, R. P., Martelli, M. F., & Zasler, N. D. (2000). Chronic pain and neuropsychological functioning. *Neuropsychology Review*, 10, 131-149.
- Iezzi, T., Duckworth, P., Vuong, L. N., Archibald, Y. M., & Klinck, A. (2004). Predictors of neurocognitive performance in chronic pain patients. *International Journal of Behavioural Medicine*, 11, 56-61.
- Jones, H., & Heldey-Whyte, E. (1983). Idiopathic hemochromatosis (IHC): Dementia and ataxia as presenting signs. *Neurology*, 33, 1479-1483.
- Kane, R. L., Gants, N. M., & DiPino, R. K. (1997). Neuropsychological and psychological functioning in chronic fatigue syndrome. *Neuropsychiatry, Neuropsychology and Behavioural Neurology*, 10, 25-31.
- Kizilbash, A. H., Vanderploeg, R. D., & Curtiss, G. (2002). The effects of depression and anxiety on memory performance. *Archives of Clinical Neuropsychology*, 17, 57-67.
- Lezak, M. D. (Ed.). (1995). *Neuropsychological Assessment*. (3rd Ed.). New York: Oxford University Press.
- Lezak, M. D., Howieson, D. B., & Loring, D. W. (Eds.). (2004). *Neuropsychological Assessment*. (4th Ed.). New York: Oxford University Press.
- Lieberman, D. A. (2004). *Learning and Memory: An Integrative Approach*. Australia: Thompson Wadsworth.
- Lieu, P. T., Heiskala, M., Peterson, P. A., & Yang, Y. (2001). The roles of iron in health and disease. *Molecular Aspects of Medicine*, 22, 1-87.
- Limdi, J. K. & Crampton, J. R. (2004). Hereditary haemochromatosis. *Quarterly Journal of Medicine*, 97, 315-324.
- Marcel, B., Komaroff, A. L., Fagioli, L. R., Kornish, J., & Albert, M. S. (1996).

- Cognitive deficits in patients with chronic fatigue syndrome. *Biological Psychiatry*, 40, 535-541.
- Martelli, M. F., Grayson, R. L., & Zasler, N. D. (1999). Posttraumatic headache: Neuropsychological and psychological effects and treatment implications. *The Journal of Head Trauma Rehabilitation*, 14, 49-69.
- Michiels, V., & Cluydts, R. (2001). Neuropsychological functioning in chronic fatigue syndrome: A review. *Acta Psychiatrica Scandinavica*, 103, 84-93.
- Milder, M. S., Cook, J. D., Stray, S., & Finch, C. A. (1980). Idiopathic Hemochromatosis, an Interim Report. *Medicine*, 59, 34-49.
- Naismith, S. L., Hickie, I. B., Turner, K., Little, C. L., Winter, P. B., Ward, K. W., Mitchell, P. & Parker, B. (2003). Neuropsychological performance in patients with depression is associated with clinical, etiological and genetic risk factors. *Journal of Clinical and Experimental Neuropsychology*, 25, 866-877.
- Nitschke, J. B., Heller, W., & Miller, G. A. (2000). Anxiety, Stress and Cortical Brain Function. In J. C. Borod (Ed.), *The Neuropsychology of Emotion*. (pp298-319). London: Oxford University Press.
- Norman, D. A., & Shallice, T. (1986) Attention To Action: Willed and automatic control of behaviour. In J. R. Davidson, G. E. Schwartz, & D. Shapiro (Eds.), *Consciousness and Self-Regulation: Advances in Research and Theory* (Vol 4). (pp 1-18). London: Plenum Press.
- Pietrangelo, A. (2003). Haemochromatosis. *Gut*, 52, 1123-1130.
- Pietrangelo, A. (2004). Medical progress: Hereditary haemochromatosis – a new look at an old disease. *The New England Journal of Medicine*, 350, 2382-2397.
- Pinero, J. & Connor, J. R. (2000). Iron in the brain: An important contributor in normal and diseased states. *The Neuroscientist*, 6, 435-453.

- Powell, L. W., & Halliday, J. W. (1985) Hemochromatosis. In Berk, J. E. (Ed.), *Gastroenterology*. (4th Ed). (pp3203-3221). London: W. B. Saunderson Company.
- Powell, L. W., George, K., McDonnell, S. M., & Kowdley, K. V. (1998). Diagnosis of Hemochromatosis. *Annals of Internal Medicine*, 129, 925-931.
- Rankin, M., Baxter, L. A., Valentine, K., & Powell, L. (2001). *A Practical Guide to Haemochromatosis (Inherited)*. Queensland: The Haemochromatosis Society Australia Inc.
- Rogers, W. A. (2000). Attention and Aging. In Park, D., & Schwarz, N. (Eds.), *Cognitive Aging: A Primer*, (pp57-73). New York: Psychology Press.
- Rholing, M. L., Green, P., Allen, L. M., & Iverson, G. (2002). Depressive symptoms and neurocognitive test scores in patients with symptom validity tests. *Archives of Clinical Neuropsychology*, 17, 205-222.
- Sachdev, P. (1993). The neuropsychiatry of brain iron. *Journal of Neuropsychiatry*, 5, 18-29.
- Sano, M. (2003). Current concepts in the prevention of Alzheimer's Disease. *CNS Spectrums*, 8, 846-853.
- Short, K., McCabe, M., & Tooley, G. (2002). Cognitive functioning in chronic fatigue syndrome and the role of depression, anxiety, and fatigue. *Journal of Psychosomatic Research*, 52, 475-483.
- Temple, R. O., Horner, M. D., & Taylor, R. M. (2004). Relationship of MMPI-2 anxiety and defensiveness to neuropsychological test performance and psychotropic medication use. *Cognition and Emotion*, 18, 989-998.
- Thompson, K. J., Shoham, S., & Connor, J. R. (2001). Iron and neurodegenerative disorders. *Brain Research Bulletin*, 55, 155-164.

- Tiersky, L. A., Johnson, S. K., Lange, G., Natelson, B. H., & DeLuca, J. (1997). Neuropsychology of chronic fatigue syndrome: A critical review. *Journal of Clinical and Experimental Neuropsychology*, 19, 560-586.
- van Zomeren, E., & Spikman, J., (2003). Assessment of Attention. In P. W. Halligan, U. Kischka & J. C. Marshall (Eds.), *Handbook of Clinical Neuropsychology*. (pp 73-88). Oxford: Oxford University Press.
- Veiel, H. O. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology*, 19, 587-603.
- Vercoulen, J. H., Baseman's, E., Swanink, C. M., Galama, J. M., Fennis, J. F., van der Meer, J. W., & Bleijenberg, G. (1998). Evaluating neuropsychological impairment in chronic fatigue syndrome. *Journal of Clinical and Experimental Neuropsychology*, 20, 144-156.
- Victor, M., Adams, R., & Cole, M. (1965). The acquired (non-Wilsonian) type of chronic hepatocerebral degeneration. *Medicine*, 44, 345-396.
- Vlaar, A. M., & Wade, T. (2003). The Adult Memory and Information Processing Battery (AMIPB) test of information-processing speed: A study of its reliability and feasibility in patients with multiple sclerosis. *Clinical Rehabilitation*, 17, 386-393.
- Waldstein, S. R., Ryan, C. M., Jennings, J. R., Muldoon, M. F., & Manuck, S. B. (1997). Self-reported levels of anxiety do not predict neuropsychological performance in healthy men. *Archives of Clinical Neuropsychology*, 6, 567-574.
- Weiland-Fiedler, P., Erickson, K., Waldeck, T., Luckenbaugh, D. A., Pike, D., Bonne,

- O., Charney, D. S., & Neumeister, A. (2004). Evidence for continuing neuropsychological impairments in depression. *Journal of Affective Disorders*, 82, 253-258.
- Wood, R. J. (2002). The 'anaemic' enterocyte in hereditary hemochromatosis: Molecular insights into the control of intestinal iron absorption. *Nutrition Reviews*, 60, 144-148.
- Zeigler, D. K., & Paolo, A. M. (1996). Self-reported disability due to headache: A comparison of clinic patients and controls. *Headache*, 36, 476-480.

Empirical Study

**Are Cognitive Processing Problems associated
with Hereditary Haemochromatosis?**

Abstract

Many people with haemochromatosis report decreased cognitive functioning as a symptom of their disease. Increasing evidence suggests that iron accumulation within the brain is involved in the pathogenesis and progression of many neurodegenerative diseases, particularly Alzheimer's Disease. Case studies have noted cognitive deficits in patients with haemochromatosis, however these patients have had advanced disease and other complicating factors such as comorbid conditions and alcohol dependence, making interpretation of findings difficult. The present study aimed to assess whether people with haemochromatosis demonstrated deficits in cognitive processes such as memory, information processing speed, attention and learning compared to matched controls. These processes are sensitive to mild and diffuse brain damage and are therefore most likely to be affected by iron-induced oxidative stress. The study included a large sample of haemochromatosis patients, a matched control group and a comprehensive neuropsychological test battery. Other factors such as depression and fatigue that are common symptoms of haemochromatosis and have been found to impact on cognitive functioning were also measured. The results of a MANOVA including all cognitive test scores indicated that participants with haemochromatosis have reduced cognitive functioning compared to controls. Individual *t* tests revealed significant deficits in motor speed as assessed by Information Processing Speed Task A. All other test scores showed no significant deficits compared to controls. Factors such as years since diagnosis, time since venesection and symptom severity were not significantly correlated with cognitive test scores, however future research is required to elucidate whether fluctuations in iron levels or other aspects of the disease influence cognitive processing.

Introduction

Many people who have haemochromatosis report cognitive problems - particularly problems with memory - as a symptom of their disease. While these complaints have often been dismissed by health professionals as resulting from fatigue or depression, there is evidence that iron-mediated damage within the brain may be responsible.

Hereditary haemochromatosis is an inherited disease in which the body absorbs too much dietary iron. It is caused by a mutation in the HFE gene named C282Y and affects approximately 1 in 200 people (Pietrangelo, 2003). The mutation causes excess iron to be absorbed and deposited in various organs, leading to oxidative damage and cell death. Common symptoms include fatigue and a general feeling of illness, liver and heart problems, abdominal pain, bronzed skin, type 2 diabetes and arthritis. These symptoms usually appear in the third to fifth decade of life.

Iron is involved in oxygen transport, cell differentiation (Lieu, Heiskala, Peterson & Yang, 2001), glucose metabolism, and the synthesis of neurotransmitters, myelin and DNA (Pinero & Connor, 2000). Iron also has the ability to cause “the conversion of hydrogen peroxide into free-radical ions that attack cellular membranes, protein and DNA” (Emerit, Beaumont & Trivin, 2001, p. 333). Iron-binding proteins such as transferrin and ferritin act as safe transport and storage systems and normally prevent this conversion. However, when these become overloaded, free iron can travel within the bloodstream to various organs in the body (Emerit et al., 2001).

Because the body's capacity to eliminate iron is limited, iron absorption is carefully controlled. Iron uptake is increased when a person is anaemic and decreased when levels are sufficient. People with haemochromatosis have a defective regulatory system that causes iron absorption to occur at 2-3 times the normal rate, even when iron stores are sufficient (Pietrangelo, 2003). How the mutation in HFE translates to increased absorption is largely unknown and it is possible that other genes are also involved (Fleming & Sly, 2002; Wood, 2002).

Iron is first absorbed within the intestine by enterocytes that are programmed to register iron levels prior to maturation. These cells receive information regarding current iron stores and needs from various independent sources (Andrews, 1999) and alter their rate of absorption accordingly. Iron is then transported across the lining of the intestine into the bloodstream.

Iron can cross the blood brain barrier and is essential to normal brain function. The brain naturally has a high iron requirement, consistent with its high energy needs (Pinero & Connor, 2000). Iron *deficiency* is associated with cell loss and decreased function within the brain and has significant and long-lasting effects on cognitive functioning (Burdo & Connor, 2002). Common consequences of iron deficiency include problems with "...cognition, motor function, dopamine-related activities and myelinogenesis..." (Connor, Menzies et al., 2001, p. 119).

The brain is negatively affected by iron overload. Excess brain iron has been associated with the pathogenesis and progression of Frederick's Ataxia, Huntington's Disease, Hallervorden-Spatz Syndrome, Parkinson's Disease and Alzheimer's

Disease (Burdo & Connor, 2002; Thompson, Shohan & Connor, 2001). Imaging studies show signs of increased iron in the basal ganglia and the choroid plexus in people with haemochromatosis (Burdo & Connor, 2002).

Case studies have indicated that cognitive deficits are often related to untreated haemochromatosis (Jones & Hedley-Whyte, 1983; Victor, Adams & Cole, 1965). Common problems associated with haemochromatosis include slowed responses, an incapacity to form ideas or think logically, poor attention span, impaired short-term memory and lack of insight into deficits. Testing with the WAIS and the WMS have revealed deficits on all tests, both verbal and visual, with severe impairments found for measures of abstract reasoning and retention of new information (Victor et al., 1965).

Cognitive deficits have also resolved when iron levels are reduced by venesection (Cutler, 1994; Milder, Cook, Stray & Finch, 1980; Tandon, Taroch & Falcon, 1988), iron-chelating drugs and/or a low-protein diet (Jones & Hedley-Whyte, 1983).

Increased iron and haemochromatosis has also been related to brain damage. Victor et al. (1965) found parenchymal damage in the cerebral cortex, white matter, basal ganglia, cerebellar cortex and dentate nucleus of their patients. Jones and Hedley-Whyte (1983) noted Alzheimer type II astrocytes in the cerebral cortex and the cerebellar dentate nucleus of one of their patients.

Few of these case studies have used comprehensive psychometric test batteries and the patients have had advanced disease, concurrent health problems and/or histories of alcohol abuse, making findings difficult to attribute to iron overload.

Many iron overload support groups list cognitive problems as a symptom of haemochromatosis. The Haemochromatosis Society Australia, Canadian Hemochromatosis Society, The Haemochromatosis Society UK, Iron Overload Diseases Association, and Iron Disorders Institute all include memory problems in their haemochromatosis literature.

If brain iron overload does negatively impact on cognitive functioning then it is important to isolate these effects from other confounding factors. Alcohol intake, medication use and other physical problems can be controlled for by excluding such participants, however other factors such as depression and fatigue are common symptoms of haemochromatosis and are therefore more difficult to control.

Pain and fatigue are common symptoms of haemochromatosis. Pain has been found to negatively impact on processing speed, attention and memory (Hart, Martelli & Zasler, 2000; DiStefano & Radanov, 1995), although some studies have found no differences between individuals with chronic pain and controls (Bell, Primeau, Sweet & Lofland, 1999). Chronic fatigue has been associated with deficits in working memory (Deluca et al., 2004), executive functioning (Marcel, Komaroff, Faioli, Kornish & Albert, 1996), learning and information processing speed (Busichio, Tiersky, Deluca & Natelson, 2004).

Depression is a frequently reported symptom of haemochromatosis, and anxiety is common during adjustment to diagnosis. Clinical depression has a negative impact on cognitive processes, particularly mental flexibility and control (Veiel, 1997). Greater severity leads to greater cognitive deficits (Airaksinen, Larsson, Lundberg, & Forsell, 2004; Elderkin-Thompson et al., 2003). Anxiety places a greater burden on the articulatory loop and central executive and competes successfully with other cognitive tasks involving these functions (Eysenck & Calvo, 1992).

The cognitive processes that are most likely to be affected by haemochromatosis, whether by iron overload or by emotional and physical factors, are those that are sensitive to brain damage. Information processing speed, attention, memory and learning are frequently affected by mild and diffuse brain damage (Lezak, Howieson & Loring, 2004).

Information processing speed underlies other cognitive functions such as attention, learning and memory (Gronwall & Sampson, 1974). It is often compromised by diffuse brain damage and is therefore likely to involve many areas of the brain (Felmingham et al., 2004; Gronwall & Sampson, 1974). Attention is primarily a function of the prefrontal cortex, although different aspects are mediated by different areas, and some elements may be impaired while others remain intact (Rogers, 2000).

Learning is defined as the ability to acquire knowledge and memory is the ability to retain it (Lieberman, 2004). Memory involves the encoding, storage and retrieval of experience and can be divided into short-term and long-term systems. It is thought

that STM is mediated by the frontal lobes and LTM is consolidated by the hippocampal structures and then stored in a distributed fashion in the neocortex (Lieberman, 2004). Baddeley (1986) extended the role of STM to include processes such as problem solving and decision-making and named it 'working memory'. This is divided into verbal and visuo-spatial memory (Della Salla, Gray, Baddeley, Allamano & Wilson, 1999).

The aforementioned cognitive processes are all interdependent; therefore tests that aim to measure one process inevitably measure aspects of some or all of them. Neuropsychological tests vary in their degree of sensitivity and specificity (Dobbs, Dobbs & Kiss, 2001). Various test batteries have been developed to maximise both sensitivity and specificity in measuring a wide range of cognitive processes. Some of the most commonly used batteries include the Wechsler Adult Intelligence Scale III (WAIS III) (Wechsler, 1997), which measures a range of intellectual abilities in both verbal and non-verbal domains, and the Wechsler Memory Scale III (WMS III) (Wechsler, 1997), which measures various aspects of memory. The Adult Memory and Information Processing Battery (AMIPB) (Coughlan & Hollows, 1985) also measures various aspects of memory and learning in both visual and verbal domains (Lezak, 1995). However, its norms are based on a British population, which is more similar to the Australian population than American norms (Clark et al., 2004) and it includes a measure of information processing speed that is more specific than other batteries as it requires less visual scanning and motor output than other similar tasks, and includes an adjustment for motor speed (Vlaar & Wade, 2003), making it ideal for populations with potential motor speed problems such as haemochromatosis.

As well as batteries for neuropsychological testing, there are specific tests designed for more detailed examinations of a particular function. For example, the

Paced Auditory Serial Addition Task (PASAT) (Gronwall & Sampson, 1974) is a widely used and highly sensitive test of attention and information processing speed (Lockwood, Linn, Szymanski et al., 2004) and the Visual Patterns Test is a relatively pure measure of visual short-term memory (Della Salla, Gray, Baddeley, Allamano & Wilson, 1999).

The effects of iron overload on cognitive functioning need to be separated from an individual's natural cognitive strengths and weaknesses. Tests such as the National Adult Reading Test can measure pre-morbid cognitive abilities (Spren & Strauss, 1998) and differentiate between 'real' deficits, caused by brain damage, and premorbid abilities that include natural strengths and weaknesses.

In summary, untreated haemochromatosis causes iron-mediated damage that affects the heart, liver, pancreas and joints, resulting in a variety of clinical symptoms.

Research has also demonstrated that iron crosses the blood brain barrier and is found in excessive amounts in the brains of people with neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. It is still debated whether excess iron accumulates in the brains of people with haemochromatosis, and if it does, whether this impacts on cognition and behaviour. Case studies have indicated that dementia, disorientation, motor problems such as ataxia and memory problems occur in conjunction with haemochromatosis, particularly in severe cases, however whether

this occurs more generally in people with haemochromatosis, and whether it is due to excess iron in the brain or other secondary effects of the disease is unknown.

There have been no studies to date investigating cognitive processes in people with haemochromatosis using a large sample, a control group and a comprehensive neuropsychological test battery. This may be partly due to the belief that the cognitive problems experienced by people with haemochromatosis are due to secondary effects of the disease such as fatigue and depression.

The present study aims to investigate whether people with haemochromatosis have poorer performances on measures of memory, learning, attention and information processing compared to matched healthy controls and if so, whether a particular pattern of deficits exists. It also aims to discover whether these problems are associated with a primary cause (excess iron) or with secondary factors such as pain, fatigue, anxiety and/or depression.

Based on the limited research in this area, the main hypotheses are:

1 - Participants with haemochromatosis may have significantly lower scores than controls on tests of memory and learning. The most sensitive tests, and therefore the most likely to show group differences in this domain, include Design Learning and List Learning.

2 – Participants with haemochromatosis may have significantly lower scores than controls on tests of attention and working memory. The PASAT is the most likely test to show significant differences as this is the most sensitive measure in this domain.

3 – People with haemochromatosis may have significantly lower scores on tests of information processing speed than controls, as measured by Information Processing Task A. Information processing speed is particularly sensitive to mild and diffuse brain damage.

4 - Deficits in cognitive processes may be due to iron overload and not specifically to anxiety/depression or fatigue.

Method

Participants

Participants were 40 adults with a diagnosis of hereditary haemochromatosis (HH), aged from 19 to 79 years, including 21 males and 19 females. Diagnoses of haemochromatosis were confirmed by participants' general practitioner and based on genetic testing. Forty healthy controls were included and the groups were matched for gender, age and years of education (details of age, education, etc. are shown in Table 1). Participants with a diagnosed mental illness, a major health problem not related to haemochromatosis or who were taking medications or other substances that are known to interfere with cognitive processes were excluded from the study. Carriers (one HFE gene mutation) were also excluded. In all cases participation was voluntary and no payment was offered for participation.

Participants were recruited through newspaper advertisements, fliers handed out at the ambulatory ward of the Royal Hobart Hospital, a television news story, an iron overload disorders support group in Hobart and through personal acquaintance.

Materials

Participants were assessed with the following measures:

Personal Data Sheet

This contained participants' basic demographic and medical details (Appendix A).

Haemochromatosis Symptom Severity Rating Scale

A visual analogue scale of 18 common haemochromatosis symptoms was used to measure symptom severity. A space was included for participants to note symptoms that did not appear on the list. Instructions specified that a mark at the beginning of the line (at zero) indicated no effect, and a mark at the end of the line (at one hundred) indicated that the symptom was 'as bad as I can imagine' (Appendix B).

Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983).

This 14-item self-report questionnaire measures anxiety and depression in non-clinical samples. Seven items are dedicated to measuring anxiety and seven to depression. It was designed to differentiate between symptoms of physical disorders and mood by excluding items that could be associated with both, such as fatigue or appetite (Pincus, Fraser & Pearce, 1998). The HADS is quick to complete and has good face validity. Both the anxiety and depression scales have good reliability and

validity and are sensitive to change (Snaith & Zigmond, 1994). Scores for anxiety and depression are calculated separately and range from 0-21 (Appendix B).

Brief Fatigue Inventory (Hann, Jacobsen, Azzarelo et al., 1998).

This 10-item self-report measure focuses on the intensity and duration of fatigue and its impact on daily activities (Hann et al., 1998). The questionnaire was modified to make it more specific to haemochromatosis and cognitive functioning; an item relating to mobility was removed and two items relating to cognitive processes were added. Scores range from 0-100 (Appendix B).

National Adult Reading Test (NART) (Nelson, 1982).

This test was used to estimate participants' premorbid intellectual abilities. Participants read aloud 50 irregularly spelled words presented in order of increasing difficulty. Test scores correlate highly (0.85) with 'g' or the general factor of intelligence (Nelson & Willison, 1982) and can be used to estimate WAIS-R full-scale IQ scores (Spren & Strauss, 1998). The NART is one of the most reliable measures of its type; reading ability is robust as it is generally preserved in people with mild to moderate dementia (Spren & Strauss, 1998) and depression (Nelson & Willison, 1982) (Appendix B).

Adult Memory and Information Processing Battery (AMIPB) (Coughlan & Hollows, 1985).

This battery of tests includes various memory, learning and information processing tasks. The AMIPB is standardised on a UK sample with four age norm groups ranging from 18-75. Scores can be used to estimate standard scores or percentiles.

Correlations between subtests are minimal, suggesting that they tap into different skills and abilities (Coughlan & Hollows, 1985). Each of the subtests included in the battery are sensitive to cognitive dysfunction (Coughlan & Hollows, 1985). The following subtests from the battery were included in the study:

Story Recall

This is primarily a measure of immediate and long-term verbal memory. Participants listen to a short story and then repeat what they remember both immediately and 30 minutes after presentation (Appendix C).

List Learning

This subtest measures verbal rote learning and memory as well as susceptibility to interference. Participants listen to and then recall a list of 15 unrelated words. After 5 trials a new (interference) list is presented and recalled, then participants are asked to recall the original list (Appendix C).

Figure Recall

This is primarily a measure of immediate and long-term visual memory. Participants copy a complex figure and then draw it from memory immediately and after 30 minutes (Appendix C).

Design Learning

This subtest measures visual rote learning, memory and susceptibility to interference. Participants are presented with a design on a 4x4 grid of dots. After 10 seconds of viewing, they reproduce the design on a blank grid. After 5 trials, a new (interference)

design is presented and recalled and then participants recall the original design (Appendix C).

Information Processing Speed Task A.

This task measures ability to mentally engage in a repetitive, speed-based task that requires sustained attention. Participants are given a sheet of paper with 105 rows of five two-digit numbers and asked to cross out the second highest number in each row. After completing a ten-item sample, they are given four minutes to complete as many of the rows as they can. Participants then complete a simple cancellation task (crossing out rows of 11's) for 20 seconds and this score is used to adjust for motor speed. This test is particularly sensitive to cerebral dysfunction (Coughlan & Hollows, 1985) (Appendix C).

The Visual Patterns Test (VPT) (Della Salla, Gray, Baddeley & Wilson, 1997).

This test measures short-term visual memory. Participants are presented with a grid on a card in which half of the squares are black. The grids range from 2x2 to 5x6 (Della Salla et al., 1999) in increasing difficulty. Participants are shown each card for 3 seconds and asked to reproduce the pattern on a blank grid of the same dimensions. When a participant fails to correctly reproduce three consecutive grids of one size, the test is discontinued. The VPT has two parallel forms. Version A, used in this study, has a test-retest reliability of .75. It is considered a comparatively pure measure of visual memory as it has a minimal spatial component (Della Salla et al., 1999) (Two examples of medium-difficulty designs are shown in Appendix C).

Paced Auditory Serial Additions Test (PASAT) (Gronwall, 1977; Gronwall & Sampson, 1974)

This test is primarily considered a test of information processing but also measures working memory capacity, executive control and sustained and divided attention (Lockwood et al., 2004). A recorded tape is played in which 60 single-digit numbers are presented at set intervals (2.0 seconds in this study). Participants are required to progressively add the last two presented numbers. The test has comprehensive norms for adult populations and is a sensitive measure of subtle, diffuse damage (Spreen & Strauss, 1998). It is widely used to assess a variety of neurological problems. The test has high reliability and validity (Lezak, 1995). Scores range from 0-60 (Appendix C).

Wechsler Adult Intelligence Scale – III (WAIS III) (Wechsler, 1997).

This test battery measures intellectual ability and is used as a diagnostic tool for neurological disorders (Wechsler, 1997). The various subscales measure verbal and visual-spatial reasoning, memory, attention and information processing speed. Two of the subtests from the WAIS are included in this study – Digit Span and Letter-Number Sequencing. Raw scores can be converted into standard scores and/or percentiles.

Digit Span

This subtest measures verbal short-term memory capacity, sequencing ability and verbal working memory. It requires participants to listen to and repeat strings of digits of increasing length. Participants perform digits forwards - repeating the sequence in order, and digits backwards – repeating the sequence in reverse order. The digits backwards task places a greater burden on working memory. The subtest has good

reliability, with test-retest estimates from .83 -.89 depending on age group (Wechsler, 1997).

Letter Number Sequencing

This test is a sensitive measure of verbal working memory. Participants are required to listen to strings of jumbled numbers and letters of increasing length and repeat them in a re-organised sequence; letters in alphabetical order followed by numbers in numerical order. Reliability estimates are good, with test-retest estimates of .70 -.80 depending on age group (Wechsler, 1997).

Procedure

Ethics approval was obtained from the Southern Tasmania Health and Medical Human Research Ethics Committee (ref H0007519). A pilot study was first undertaken with four participants - two with a diagnosis of haemochromatosis and two controls. The aims of the pilot study were to determine the presentation order of the tests and ensure that participants understood the questionnaires. No problems were noted in the pilot study.

Participants with haemochromatosis were asked to complete the assessment at least two weeks post-venesection, as fatigue is common for a few days after treatment. A small amount of participants were having venesection weekly and these participants were tested just prior to venesection. The mean period of time post-venesection was 10 weeks (range 1-36). Participants were tested at a time suitable to them, usually in the morning when they felt most alert. Each block of tests took approximately half an hour to complete and a ten-minute break was given between blocks.

Assessments were conducted in a consulting room either at the University Psychology Clinic or at the Department of Psychiatry at the Royal Hobart Hospital. Participants who lived in the North of the state were visited in their homes.

Participants read the information sheet and signed the consent form (see Appendix D) before completing the Personal Data Sheet and the Haemochromatosis Symptoms Rating Scale, Brief Fatigue Inventory and the HADS.

The NART was administered prior to a block of primarily verbal or visual-spatial subtests. Participants were then given a break before completing the second block of subtests. One block consisted of (in order) Stories subtest, List Learning, Digit Span, Letter Number Sequencing and then Delayed Recall of the Stories subtest. The other block included Complex Figure, Visual Patterns Test, Design Learning, Paced Auditory Serial Addition Test, Information Processing Task A and then the Delayed Recall of the Complex Figure subtest. The blocks were administered in counterbalanced order.

Design and Data Analysis

This study employed a between groups design using independent samples *t* tests to assess between-group differences for self-report variables and a MANOVA to assess between-group differences for cognitive variables (Tabacknick & Fidell, 2001). Cognitive variables were further analysed using independent samples *t* tests.

Pearson Product-Moment correlations were used to investigate the relationships between self-report and cognitive variables to see whether specific self-report variables negatively impacted on cognition.

A power analysis was conducted using a standard methodology (Lenth, n.d.) and a sample of 40 participants in each group was considered adequate. An alpha level of .01 was chosen for correlations and *t* tests for cognitive variables as a large number of measures were included, increasing the risk of Type 1 errors. An alpha level of .05 was chosen for *t* tests of self-reported variables as this is the conventional value recommended for statistical tests (Tilley, 1994).

Results

Self-report measures

The means and standard deviations for each of the self-report variables are shown in Table 1.

Table 1

Means and standard deviations (in parentheses) for self-report participant variables

Self-Report Variable	Haemochromatosis		Control	
Age	54.2	(11.4)	54.3	(10.9)
Education Level	11.8	(2.7)	12.8	(2.6)
NART score	104.0	(9.0)	105.8	(7.1)
Haemochromatosis Symptom Score	360.7	(230.9)	223.9	(166.3)
Brief Fatigue Inventory Score	31.1	(22.6)	22.3	(18.6)
Anxiety (HADS) Score	6.4	(3.9)	5.7	(3.5)
Depression (HADS) Score	4.5	(3.9)	2.8	(3.2)
Years Since Diagnosis (HH only)	4.7	(4.3)		
Weeks Since Venesection (HH only)	10.0	(8.8)		

A significant difference was noted between the two groups for self-reported haemochromatosis symptom severity $t(78) = 3.04, p < .05$. Participants with haemochromatosis reported significantly higher symptom severity than controls. There was also a significant difference noted between groups for self-rated depression $t(78) = 2.19, p < .05$. Participants with haemochromatosis reported higher rates of depression, although both groups' scores were well below the cut-off for clinical depression, where 'mild depression' scores are 8-10 (Snaith & Zigmond, 1994).

Relationship between self-report and cognitive measures

Pearson Product-Moment correlations were performed to investigate whether the self-reported variables were related to cognitive test scores. This data is shown in Table 2 (see Appendix E).

A significant positive correlation was found between level of education and delayed story recall ($r = .33$). Depression had a significant negative effect on Complex Figure-percentage retained ($r = -.30$). A significant negative correlation was found between symptom severity and Design Learning trials A1-A5. The remaining self-report scores were not significantly correlated with cognitive test scores.

Many significant correlations were also noted between self-report variables (see Table 2).

Cognitive Measures

The means and standard deviations for the cognitive test results are presented in Table 3. All scores are given as percentiles, with the exception of List Learning percentage lost and Design Learning percentage lost. These scores were calculated by the formula $A5 - A6 / A5 \times 100$ and are measures of percentage of words/lines lost after the interference task was presented.

Table 3

Means and standard deviations (in parentheses) of cognitive variables for participants with and without haemochromatosis

Cognitive Test Score	Haemochromatosis		Control	
	N = 40		N = 40	
Story Recall (Immediate Recall)	48.5	(28.4)	46.8	(28.7)
Story Recall (Delayed Recall)	45.7	(27.6)	44.0	(30.8)
Digit Span	44.4	(20.3)	55.3	(27.1)
Letter Number Sequencing	47.2	(22.9)	55.7	(24.6)
Paced Auditory Serial Addition Test	37.0	(10.1)	41.1	(10.3)
List Learning Trials 1-5	43.4	(27.5)	45.8	(30.1)
List Learning Percentage Lost in Recall	20.2	(13.7)	19.9	(14.2)
Complex Figure Copy	65.6	(18.9)	69.8	(10.3)
Complex Figure Immediate Recall	75.8	(21.0)	69.2	(21.9)
Complex Figure Delayed Recall	72.0	(22.3)	68.8	(24.3)
Design Learning Trials 1-5	45.0	(29.7)	56.2	(31.2)
Design Learning Percentage lost in Recall	15.7	(25.1)	17.8	(24.7)
Visual Patterns Test	44.8	(22.8)	40.6	(23.0)
Information Processing Motor Speed	41.1	(29.4)	62.0	(23.3)
Information Processing Adjusted Score	61.7	(25.9)	69.6	(27.4)

A MANOVA was initially performed to investigate overall differences between the two groups. The result was significant, Pillai's Trace = .985, $F(15, 47) = 200.10$, $p <$

.01. Participants with haemochromatosis performed more poorly on measures of cognitive processing than controls.

Independent samples t tests were performed to assess between-group differences for the cognitive test scores.

A significant difference was found for motor speed as measured by information processing Task A $t(78) = -3.51, p < .01$. The haemochromatosis group was significantly slower than the control group on this simple speed-based cancellation task. No other significant differences were found between the two groups for cognitive test scores.

Because Digit Span scores approached significance, $t(77) = -2.02, p < .05$, scores were divided into Digits Forwards and Digits Backwards, as the two components are proposed to measure slightly different abilities (Lezak, 1995).

There was a non-significant difference between groups on both tasks. The haemochromatosis group performed slightly better than the control group on digits forwards, recalling a mean score of 6.57 digits compared to 6.51 digits for the control group, $t(1,72) = .19, p = .85$. The control group performed better than the haemochromatosis group on digits backwards, recalling a mean of 4.95 digits compared to 4.46 for the haemochromatosis group, $t(1,72) = 1.90, p = .06$.

Discussion

This study aimed to investigate whether people with haemochromatosis demonstrated deficits on measures of attention, information processing speed, learning and memory compared to healthy controls. Consistent with the limited research in this field, it was hypothesised that people with haemochromatosis would perform more poorly than controls in these cognitive domains. This hypothesis was supported, as participants with haemochromatosis achieved significantly lower scores than controls on the cognitive tests as a whole.

More specifically, hypothesis 1 was that people with haemochromatosis would have significantly lower scores on tests of memory and learning and that this would most likely be demonstrated in test results from Design Learning and List Learning. This hypothesis was not supported, as there were no significant differences any measures of learning and memory when the test scores were analysed individually.

Hypothesis 2 was that people with haemochromatosis would have significantly lower scores than controls on tests of attention and working memory, and that this would be most evident on scores from the PASAT. This hypothesis was not supported, as there were no significant between-group differences on measures of attention and working memory when the tests were analysed individually. There was a trend, however, for people with haemochromatosis to perform more poorly on Digit Span. This finding will be further discussed below.

Hypothesis 3 was that people with haemochromatosis would achieve significantly lower scores on tests of information processing speed than controls, as measured by Information Processing Task A. This hypothesis was partially supported. There was not a significant difference between groups for information processing speed after an adjustment was made for motor speed. However, motor speed itself was significantly slower in participants with haemochromatosis than controls.

Hypothesis 4 was that any deficits in cognitive processes would not be due specifically to anxiety/depression or fatigue. This hypothesis was for the most part supported as correlations between cognitive test scores and self-reported variables such as fatigue, anxiety and depression were generally non-significant. However, there were three exceptions for self-reported depression, which will be discussed below.

The evidence in the literature for impaired cognitive functioning in people with haemochromatosis was mainly based on physiological data and anecdotal evidence. The few studies that have investigated cognitive functioning in people with haemochromatosis did not include control groups and few reported neuropsychological test data. Therefore, it is difficult to compare the results of this study with those of previous studies.

The cognitive deficits in the haemochromatosis group were minor and generalised, as it was only when scores from all cognitive tests were combined that a significant difference between the groups could be detected. There was a small between-group difference for each cognitive measure and these were in the same direction, with few

exceptions, indicating that there is no specific pattern of deficits associated with haemochromatosis, but rather a generalised reduction in attention, memory, learning and information processing speed.

There was a significant difference in motor speed between the groups. This is not surprising given the basal ganglia is the target of iron overload in many neurological diseases (Burdo & Connor, 2002). Neuroimaging studies have indicated that iron levels are elevated in the basal ganglia (Burdo & Connor, 2002; Connor et al, 2001; Pinero & Connor, 2000), which is responsible for the initiation and coordination of movement (Lezak et al., 2004). Case studies of people with haemochromatosis have noted psychomotor retardation (Milder et al., 1980), ataxia, jerky movements, rigidity and poor hand coordination (Jones & Hedley-Whyte, 1983) as symptoms of haemochromatosis. Patients with Wilson's Disease, in which copper levels are elevated within the basal ganglia, also display slow motor speed responses in test situations (Littman, Medalia, Senior & Scheinberg, 1995). However, another explanation for slowed motor speed in haemochromatosis may be a high prevalence of arthritis, which is a common symptom of haemochromatosis and is particularly prevalent in the hands (Milder et al., 1980).

There was a trend for participants with haemochromatosis to perform more poorly than controls on the Digit Span subtest. Further analysis indicated that digits backwards, rather than digits forwards, best differentiated the two groups although there was not a significant difference between digits forwards and backwards scores. Digit Span is a measure of attentional capacity, as increasing amounts of information are stored in working memory. Digits Backwards includes an additional component to

Digits Forwards in that participants manipulate as well as retain information by rearranging the digits upon recall. Digit Span is considered to be a less sensitive measure than the PASAT, however the two tests measure different aspects of attention and working memory. The PASAT measures information processing speed and attention and is not a measure of capacity as it only requires participants to add two digits at a time, whereas Digit Span is primarily a measure of capacity. Letter-Number Sequencing is also similar to Digit Span, particularly the backwards component, as it also measures working memory capacity and has a manipulation component and no significant difference was noted for this test. Another measure of visual capacity, the Visual Patterns Test, also showed no significant between-group differences. It may be that this finding is due to Type 1 error rather than a real between-groups difference.

A significant positive correlation was found between level of education and delayed story recall ($r = .33$) and there was a trend for education to be positively correlated to immediate story recall. It is common for education to have a positive influence on test scores in nearly all domains (Lezak, 1995), although many tests, such as the Visual Patterns Test, include adjustments for education that aim to reduce its effect on test results (Della Salla et al., 1999). Symptom severity was significantly related to performance on the Design Learning trials A1-A5. Participants with less severe haemochromatosis symptoms performed better on the learning trials than those with more severe symptoms, however retention (percentage retained) was not affected.

Depression had a significant negative effect on Complex Figure percentage retained which measures the amount of information lost between immediate and delayed recall

($r = -.30$). There was also a non-significant trend for depression to negatively impact on Story Recall immediate and delayed scores. These findings are consistent with those reported in Veiel's (1997) review where approximately 15% of depressed individuals performed significantly more poorly than controls on tests involving recall of complex figures and stories (Veiel, 1997).

Significant correlations were also noted between various self-report variables. Participants who reported high levels of haemochromatosis symptoms tended to report higher levels of anxiety, depression and fatigue. As the symptoms of each of these constructs tend to overlap, this result was expected.

Participants with haemochromatosis reported significantly higher symptom severity than controls, indicating that they were affected by symptoms of the disease. They also reported significantly higher depression scores. However, both groups reported low depression scores compared to clinical samples and neither group was classified as clinically depressed (Snaith & Zigmond, 1994). Because all participants who reported clinical psychological or physical health problems were excluded from the study, the effects of these on cognitive test scores were expected to be minimal.

There are several possible reasons why few significant differences were found between participants with haemochromatosis and controls on the cognitive measures. One possibility is that the cognitive tests were not sensitive enough to pick up subtle differences between the groups. However, the measures that were used are considered to be highly sensitive to brain damage and are able to determine subtle and diffuse

damage in cases such a mild concussion. Therefore, they should have been able to detect real between-group differences if they existed.

The choice of statistical tests or number of participants may have affected the power to detect real differences between the groups. However, a power analysis determined that 40 participants in each group would be sufficient to detect any real between-group differences. Because of the lack of previous research, this study aimed to measure a wide range of cognitive processes and as such, many cognitive test scores were included in analysis. To reduce the likelihood of Type 1 errors, an alpha level of .01 was nominated. This may have increased the likelihood of Type 2 errors, however only one cognitive test (Digit Span) reached significance at the less stringent .05 alpha level.

Another possibility is the selection of participants. Participants were volunteers and opted to complete the tests knowing that their cognitive functions were being measured. Two participants in the haemochromatosis group found the test battery too difficult and chose not to continue. Their data was not included in the study. There may have been other potential participants with haemochromatosis who felt that their cognitive processes were impaired and decided not to volunteer for the study due to the potential for failure on the tests.

The haemochromatosis group was also heterogenous – the disease has a wide range of symptoms, participants had been diagnosed for varying amounts of time and were at different stages of treatment. All haemochromatosis participants had no other major health problems and most were currently experiencing few symptoms of

haemochromatosis. However, some participants had been diagnosed early and would have had elevated iron levels for only a short period of time, while others had been diagnosed late in life, experienced severe symptoms and had had severely elevated iron levels. Iron levels were not measured in this study, so it is difficult to explore the relationships between iron levels and cognitive performance. Efforts were made to elucidate whether time since diagnosis, time since venesection and symptom severity influenced test scores, and no significant correlations were found. However, it remains that some participants may have experienced real problems with cognition while others didn't, just as some haemochromatosis patients have arthritis or heart problems and others don't. Analysing group results as a whole may have masked the scores of some impaired individuals.

The control group also consisted of volunteers and most of these were known to the researcher. The control group and the haemochromatosis group both performed below expected levels on tests of verbal and visual-spatial learning. Participants in the control group may have been more anxious about their performance as they were familiar with the experimenter, despite being reassured that all test scores were confidential, and this may have impacted on their performance on some of the cognitive tests.

This study did not include a measure of pain and therefore could not investigate its effects on cognitive functioning. It has been well documented that severe pain can impair cognitive functions, particularly information processing speed, attention and memory (DiStefano & Radanov, 1995; Hart et al., 2000). It is unlikely that the majority of haemochromatosis participants experienced pain severe enough to impact

on cognitive functioning, however investigating the influence of pain on motor speed, particularly, may have helped to elucidate whether this significant finding was due to cognitive factors or arthritis. The study also did not include a test of effort. Rohling, Green, Allen and Iverson (2002) suggest that using tests of effort and symptom validity tests help to differentiate between reported and real deficits in cognitive functioning and it would be useful to include these measures in future research.

Further research is required to investigate a number of questions raised by this study. Is motor speed impaired in people with haemochromatosis and is it due to the cognitive control of motor functioning or to physical factors such as pain or swollen joints? Is there a capacity problem in working memory in people with haemochromatosis, as suggested by the results from the Digit Span subtest? Do factors such as previous and current iron levels, treatment regime or constellation of symptoms relate to cognitive abilities? Do carriers, who have elevated iron levels without overt symptoms, experience cognitive problems?

A study using repeated measures, for example pre and post venesection, rather than a control group could avoid the recruitment problems experienced in this study and hence the difficulty of participants' familiarity with the experimenter. If a control group was required, using a researcher who was blind to participants' diagnostic status may also control for possible confounding effects that may have occurred in this study.

It also remains that the significant findings of this study may be due to an aspect of the disease other than increased iron levels in the brain. The liver is one of the first

points of iron overload in haemochromatosis due to its naturally high iron content. Liver disease can impair attention and processing speed while having little impact on memory and conceptual abilities (Lezak et al., 2004). A more detailed analysis of symptoms in future studies may help to separate other possibilities from that of increased brain iron.

In conclusion, in 1980 Milder et al. noted in a review of haemochromatosis patients that “Neurologic symptoms have impressed us more than would be suggested by the general literature...but have received little attention since then.” (Milder et al., 1980, p. 44). This study aimed to address this gap in the literature by assessing cognitive functioning in people with haemochromatosis using a comprehensive neuropsychological test battery and a matched control group. Significant between-group differences were found with haemochromatosis patients achieving lower scores overall for the cognitive tests. When the tests were analysed individually, the most prominent difference was in motor speed, with Digit Span showing a trend towards significance. Whether these differences are due to iron overload within the brain or some other factor is still unknown and further research is required to confirm and further investigate the current findings.

References

- Airaksinen, E., Larsson, M., Lundberg, L., & Forsell, Y. (2004). Cognitive functions in depressive disorders: evidence from a population-based study. *Psychological Medicine, 34*, 83-91.
- Andrews, N. C. (1999). Disorders of iron metabolism. *The New England Journal of Medicine, 341*, 1986-1995.
- Baddeley, A. D. (1986). *Working Memory*. Oxford: Clarendon Press.
- Bell, B. D., Primeau, M., Sweet, J. J., & Lofland, K. R. (1999). Neuropsychological functioning in migraine headache, nonheadache chronic pain, and mild traumatic brain injury patients. *Archives of Clinical Neuropsychology, 14*, 389-399.
- Burdo, J. R., & Connor, J. R. (2002). Iron Transport in the central nervous system. In D. M. Templeton (Ed.), *Molecular and Cellular Iron Transport*. (pp. 487-508). New York: Marcel Dekker, Inc.
- Busichio, K., Tiersky, L. A., Deluca, J., & Natelson, B. H. (2004). Neuropsychological deficits in patients with chronic fatigue syndrome. *Journal of International Neuropsychological Society, 10*, 278-285.
- Canadian Hemochromatosis Society. (n.d.). *What are the Symptoms*. Retrieved April 7, 2005, from <http://www.cdnhemochromatosis.ca/>
- Clark, M. S., Dennerstein, L., Elkardi, S., Guthry, J. R., Bowden, S. C., & Henderson, V. W. (2004). Normative data for tasks of executive function and working memory for Australian born women aged 56-67. *Australian Psychologist, 39*, 244-250.

- Connor, J. R., Menzies, S. L., Joseph, R., Burdo, B. A. & Boyer, P. (2001). Iron and iron management proteins in neurobiology. *Paediatric Neurology*, 25, 118-129.
- Cutler, P. (1994). Iron overload and psychiatric illness. *Canadian Journal of Psychiatry*, 39, 8-11.
- Coughlan, A. K., & Hollows, S. (1985). *The Adult Memory and Information Processing Battery Test Manual*. Leeds: St James's University Hospital.
- Della Salla, S., Gray, C., Baddeley, A., & Wilson, L. (1997). *The Visual Patterns Test: A new test of short-term visual recall*. Suffolk: Thames Valley Test Company.
- Della Salla, S., Gray, C., Baddeley, A., Allamano, N., & Wilson, L. (1999). Pattern span: a tool for unwinding visuo-spatial memory. *Neuropsychologia*, 37, 1189-1199.
- Deluca, J., Christodoulou, C., Diamond, B. J., Rosenstain, E. D., Kramer, N., & Natelson, B. H. (2004). Working memory deficits in chronic fatigue syndrome: Differentiating between speed and accuracy of information processing. *Journal of the International Neuropsychological Society*, 10, 101-109.
- Di Stefano, G., & Radanov, B. P. (1995). Course of attention and memory after common whiplash: A two-years prospective study with age, education and gender pair-matched patients. *Acta Neurologica Scandinavica*, 91, 346-352.
- Dobbs, B.M., Dobbs, A. R., & Kiss, I. (2001). Working memory deficits associated with chronic fatigue syndrome. *Journal of the International Neuropsychological Society*, 7, 285-293.

- Elderkin-Thompson, V., Kumar, A., Bilker, W. B., Dunkin, J. J., Mintz, J., Moberg, P. J., Mesholam, R. I., & Gur, R. E. (2003). Neuropsychological deficits among patients with late-onset minor and major depression. *Archives of Clinical Neurology*, 18, 529-549.
- Emerit, J., Beuamont, C., & Trivin, F. (2001). Iron metabolism, free radicals, and oxidative injury. *Biomedical Pharmacotherapy*, 55, 333-339.
- Eysenck, M. W., & Calvo, M. G. (1992). Anxiety and performance: The processing Efficiency theory. *Cognition and Emotion*, 6, 409-434.
- Felmingham, K. L., Baguley, I. K., & Green, A. M. (2004). Effects of diffuse axonal injury on speed of information processing following severe traumatic brain injury. *Neuropsychology*, 18, 564-571.
- Fleming, R. E., & Sly, W. S. (2002). Mechanisms of iron accumulation in hereditary hemochromatosis. *Annual Review of Physiology*, 64, 663-680.
- Gronwall, D. M. A., & Sampson, H. (1974). *The Psychological Effects Of Concussion*. New Zealand: Auckland University Press/Oxford University Press.
- Hart, R. P., Martelli, M. F., & Zasler, N. D. (2000). Chronic pain and neuropsychological functioning. *Neuropsychology Review*, 10, 131-149.
- Haemochromatosis Society Australia Inc. (n.d.). *Haemochromatosis...* [Brochure]. Haemochromatosis Society Australia: Author.
- Hann, D. M., Jacobsen, P. B., Azzarello, L. M., Martin, S. C., Curran, S. L., Fields, K. K., Greenberg, H., & Lyman, G. (1998). Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. *Quality of Life Research*, 7, 301-310.

- Iron Disorders Institute. (n.d.). *Disorders: Hemochromatosis Introduction*. Retrieved April 7, 2005, from <http://www.irondisorders.org/disorders/hem/>
- Iron Overload Diseases Association, Inc. (n.d.). *16 Facts You Should Know*. Retrieved April 7, 2005, from <http://www.ironoverload.org/facts.html>
- Jones, H., & Heldestad-Whyte, E. (1983). Idiopathic hemochromatosis (IHC): Dementia and ataxia as presenting signs. *Neurology*, 33, 1479-1483.
- Lenth, R. (n.d.). *Java applets for Power and Sample Size*. Retrieved April 18, 2005, from <http://www.stat.uiowa.edu/~lenth/power/>
- Lezak, M. D. (1995). *Neuropsychological Assessment*. (3rd Ed.). Oxford: Oxford University Press.
- Lezak, M. D., Howieson, D. B., & Loring, D. W. (Eds.). (2004). *Neuropsychological Assessment*. (4th Ed.). New York: Oxford University Press.
- Littman, E., Medalia, A., Senior, G., & Scheinberg, I. H. (1995). Rate of information processing in patients with Wilson's Disease. *Journal of Neuropsychiatry*, 7, 68-71.
- Lieberman, D. A. (2004). *Learning and Memory: An Integrative Approach*. Australia: Thompson Wadsworth.
- Lieu, P. T., Heiskala, M., Peterson, P. A., & Yang, Y. (2001). The roles of iron in health and disease. *Molecular Aspects of Medicine*, 22, 1-87.
- Lockwood, A. H., Linn, R. T., Szymanski, H., Coad, M. L. & Wack, D. S. (2004). Mapping the neuronal systems that mediate the Paced Auditory Serial Addition Task (PASAT). *Journal of International Neuropsychological Society*, 10, 26-34.
- Marcel, B., Komaroff, A. L., Fagioli, L. R., Kornish, J., & Albert, M. S. (1996).

- Cognitive deficits in patients with chronic fatigue syndrome. *Biological Psychiatry*, 40, 535-541.
- Milder, M. S., Cook, J. D., Stray, S., & Finch, C. A. (1980). Idiopathic Hemochromatosis, an Interim Report. *Medicine*, 59, 34-49.
- Nelson, H. E. & Willison, J. (1982). *National Adult Reading Test (NART) Test Manual*. (2nd Ed.) Part II. Berkshire: NFER-Nelson.
- Norman, D. A., & Shallice, T. (1986) Attention To Action: Willed and automatic control of behaviour. In J. R. Davidson, G. E. Schwartz, & D. Shapiro (Eds.), *Consciousness and Self-Regulation: Advances in Research and Theory (Vol 4)*. (pp 1-18). London: Plenum Press.
- Pietrangelo, A. (2003). Haemochromatosis. *Gut*, 52, 1123-1130.
- Pincus, T., Fraser, L., & Pearce, S. (1998). Do chronic pain patients 'stroop' on pain stimuli? *British Journal of Clinical Psychology*, 37, 49-58.
- Pinero, D. J., Hu, J., & Connor, J. R. (2000). Alterations in the interaction between iron regulatory proteins and their iron responsive element in normal and alzheimer's diseased brains. *Cellular and Molecular Biology*, 46, 761-776.
- Rholing, M. L., Green, P., Allen, L. M., & Iverson, G. (2002). Depressive symptoms and neurocognitive test scores in patients with symptom validity tests. *Archives of Clinical Neuropsychology*, 17, 205-222.
- Rogers, W. A. (2000). Attention and Aging. In Park, D., & Schwarz, N. (Eds.), *Cognitive Aging: A Primer*, (pp57-73). New York: Psychology Press.
- Snaith, R. P., & Zigmond, A. S. (1994). *The Hospital Anxiety and Depression Scale with The Irritability-Depression-Anxiety Scale and The Leeds Situational Anxiety Scale Manual*. Berkshire: NFER-Nelson.
- Spreen, O., & Strauss, E. (1998). *A Compendium of Neuropsychological Tests:*

Administration, Norms and Commentary. (2nd Ed.). Oxford: Oxford University Press.

Tabacknick, B. G., & Fidell, L. S. (2001). *Using Multivariate Statistics (4th Ed.).* Boston: Allyn & Bacon.

Tandon, R., Taroch, J., & Falcoh, S. (1988). Hemochromatosis with episodic confusion. *Journal of Clinical Psychiatry, 19*, 284.

Thompson, K. J., Shoham, S., & Connor, J. R. (2001). Iron and neurodegenerative disorders. *Brain Research Bulletin, 55*, 155-164.

Tilley, A. (1994). *An Introduction to Psychological Research and Statistics (2nd Ed.).* Brisbane: Pineapple Press.

The Haemochromatosis Society UK. (n.d.). *Haemochromatosis: An Iron Overload Disorder.* Retrieved April 7, 2005, from <http://www.ghsoc.org/home.html>

Veiel, H. O. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology, 19*, 587-603.

Vlaar, A. M., & Wade, T. (2003). The Adult Memory and Information Processing Battery (AMIPB) test of information-processing speed: A study of its reliability and feasibility in patients with multiple sclerosis. *Clinical Rehabilitation, 17*, 386-393.

Wechsler, D. (1997). *WAIS III Manual.* New York: The Psychological Corporation.

Wood, R. J. (2002). The 'anemic' enterocyte in hereditary haemochromatosis: Molecular insights into the control of intestinal iron absorption. *Nutrition Reviews, 60*, 144-148.

Table of Appendices

Appendix A: Personal Data Sheet	76
Appendix B: Self-Report and Demographic Data forms	79
Appendix C: Cognitive Tests	84
Appendix D: Information Sheet and Consent Form	93
Appendix E: Table 2. Correlations for self-report and cognitive variables	97

Appendix A
Personal Data Sheet

Personal Data Sheet

Date: ____/____/____

Participant ID number: _____

Name: _____

Address: _____

Postcode: _____

Phone: Home _____ Work _____ Other _____

Date of Birth: ____/____/____

Gender (Please circle) Male / Female

Level of Education Achieved _____

Are you suffering from a psychological disorder? (Please circle) Yes / No

If 'Yes' please specify: _____

Does this condition affect your memory or thinking?

Do you have any physical health problems other than Haemochromatosis?
(Please circle) Yes / No

If 'Yes' please specify: _____

Does this affect your memory or thinking?

Are you taking any medications? (Please circle) Yes / No

If 'Yes' please specify: _____

Have you stopped taking any medication in the last 3 months (Please circle)
Yes / No

If yes, please specify: _____

Have you been diagnosed with Haemochromatosis?

If Yes

When was this diagnosis made? _____

Who diagnosed you? _____

Are you currently having treatment? Yes / No

Please outline treatment type and frequency (e.g. venesections every three months)

When was your last venesection? _____

As you know we need to contact the medical practitioner who diagnosed you with HH to confirm this diagnosis, if you consent to this (as per consent form) please provide the following information.

Name of Medical Practitioner _____

Address _____

Phone Contact: _____

If No

Have you been tested for Haemochromatosis (that is has a Dr checked your iron levels or done a genetic test)? Yes / No

Has anyone in your family been diagnosed with Haemochromatosis?
Yes / No

Appendix B

Self-Report and Demographic Data forms:

Haemochromatosis Symptom Severity Rating Scale

Hospital Anxiety and Depression Scale

Brief Fatigue Inventory - Revised

National Adult Reading Test

The following items from the list above have been removed for copyright or proprietary reasons:

Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983)

Brief Fatigue Inventory (Hann, Jacobsen, Azzarelo et al., 1998)

National Adult Reading Test (NART) (Nelson, 1982)

Haemochromatosis Symptom Severity Rating Scale

Please rate to what extent you experience the following symptoms by placing a mark on the line (from 0 - not at all affected to 100 – as bad as I can imagine)

	0	100
Lethargy	<hr/>	
Heart Problems	<hr/>	
Forgetfulness	<hr/>	
Skin Lesions	<hr/>	
Liver Problems	<hr/>	
Loss of Body Hair	<hr/>	
Irritability	<hr/>	
Arthritis	<hr/>	
Depression	<hr/>	
Itchiness	<hr/>	
Inability to Concentrate	<hr/>	
Abdominal Discomfort	<hr/>	
Anxiety	<hr/>	
Bronzed Complexion	<hr/>	
Loss of Sex Drive	<hr/>	
Diabetes	<hr/>	
Weakness	<hr/>	
Weight Loss	<hr/>	
Other (Please Specify)	<hr/>	
-	<hr/>	
-	<hr/>	
-	<hr/>	

Appendix C

Cognitive Tests

Story Recall

List Learning lists A and B

Figure Recall – Complex Figure

Design Learning Designs A and B

Information Processing Speed Task A

Visual Patterns Test

Paced Auditory Serial Addition Test

The following items from the list above have been removed for copyright or proprietary reasons:

Story Recall; List Learning lists A and B; Figure Recall - Complex Figure; Design Learning Designs A and B; Information Processing speed Task A. The source for all these tests is: Adult Memory and Information Processing Battery (AMIPB) (Coughlan & Hollows, 1985)

Also removed is:

The Visual Patterns Test (VPT) (Della Sala, Gray, Baddeley & Wilson, 1997), and

Paced Auditory Serial Additions Test (PASAT) (Gronwall, 1977; Gronwall & Sampson, 1974)

Appendix D

Information Sheet and Consent Form



Information Sheet
Does Haemochromatosis affect memory?

Chief Investigators: Lisa Gilroy, Iain Montgomery & Clive Skilbeck

Research Student: Gayle McElwee

Purpose of the Study:

People who have genetic haemochromatosis store too much iron in their bodies. Excess iron can be deposited in various organs in the body such as the liver, heart and joints. This excess iron is toxic and causes damage to these organs. It is thought that excess iron can also cross the blood-brain-barrier and affect thought processes such as memory. The purpose of this study is to investigate whether people with haemochromatosis achieve significantly lower scores on measures of memory, learning, attention and/or processing speed, compared to a control group who do not have a diagnosis of haemochromatosis.

Criteria for Inclusion:

We are looking for 40 people who are aged 18+ who have a definite diagnosis of haemochromatosis (this will need to be confirmed by your medical practitioner). We also need 40 people who do not have a diagnosis of haemochromatosis and are otherwise healthy. We will try to match the two groups by age, gender and years of education.

Study Procedures:

The assessment will take place in a private, quiet room at the University Psychology Clinic, which is located at the University of Tasmania, School of Psychology (Annexe), Churchill Avenue, Sandy Bay. The date and time of the appointment, which has been discussed and tentatively booked, will be confirmed by phone or email one day prior to the assessment session. If required, further directions to the clinic will be given at this time.

You will be asked to read the information sheet and sign the consent form, then fill in three questionnaires relating to your health.

You will then participate in a series of tests that assess aspects of cognitive ability; memory, attention, learning and processing speed.

When the cognitive assessment is completed, you will be given brief feedback about your performance. You will also have a chance to ask questions.

The entire session should take just over an hour. The cognitive/memory assessment should take 60 minutes and completing questionnaires 10 minutes.

Possible Benefits:

The results of this study should indicate whether people with haemochromatosis suffer from memory/attention problems. If this is the case, then teaching these people

strategies to improve their abilities may be beneficial. This study may also help to raise public awareness of haemochromatosis and its possible effects, which may lead to a greater emphasis on early screening and prevention.

Confidentiality:

Your responses to the questionnaires and the results from your cognitive assessment will not be identifiable by name. All questionnaires and cognitive test results will be kept in a locked filing cabinet within the Psychology Department at the University of Tasmania for five years, after which they will be destroyed.

Freedom to Refuse or Withdraw:

As you are a volunteer in this study, you are able to refuse to participate or withdraw from the procedure at any time, for any reason, without prejudice.

Withdrawal of a participant from the Project by the Investigators:

If at any time it seems evident that you are unduly distressed by any procedure, the assessment process will be discontinued.

Approval:

This project has received ethical approval from the Southern Tasmania Social Sciences Human Research Ethics Committee.

Contact Persons:

Investigator: Gayle McElwee. ph 62261808 or email mcelweeg@utas.edu.au

Supervisor: Lisa Gilroy. ph 62264886, or email ljgilroy@utas.edu.au

Supervisor: Iain Montgomery. ph 6226-3846, or email Iain.Montgomery@utas.edu.au

Supervisor: Clive Skilbeck. ph 6226-7459, fax: 6226-2883, or email Clive.Skilbeck@utas.edu.au

Concerns or Complaints:

You may contact the 'Contact Persons' or the Southern Tasmania Social Sciences Human Research Ethics Committee:

Chair – Associate Professor Gino Del Pont Ph 62262078

Or Executive Officer – Amanda McAully. Ph 62262763

Results of Investigation: Individual results will not be available, as questionnaire data is not identified by name. However, group data from the study will be available on request, and will be available on the University homepage at the completion of the study. Link: www.utas.edu.au

Please keep a copy of this form so that you can contact the above people if necessary.



UNIVERSITY
OF TASMANIA

School of Psychology

Consent Form

Does Haemochromatosis affect memory?

Investigators: Lisa Gilroy, Iain Montgomery, Clive Skilbeck, Gayle McElwee

Statement By Participant:

I have read and understood the 'Information Sheet' for this study.
The nature and possible effects of the study have been explained to me.

I understand that the study involves the following procedures:

- Filling in three questionnaires relating to my health (approx 10 minutes).
- Completing a series of tests designed to measure my thought processes including my memory, processing speed, learning and attention (approx 60 minutes).

I understand that the content of the questionnaires may be sensitive, as they relate to my perceptions of my health. The results of the memory assessment may also be disappointing if they are not parallel with my expectations.

I understand that I will not be given detailed feedback regarding my results on tests concerning my memory, processing speed, learning and attention, but rather general brief feedback.

I understand and consent to my medical practitioner being contacted to confirm my diagnosis of haemochromatosis (if applicable).

I have been informed that the results of the study may not be of any direct benefit to my medical management.

Any questions that I have asked have been answered to my satisfaction.

I agree that research data gathered for the study may be published provided that I cannot be identified as a participant.

I understand that research data will be securely stored in a locked filing cabinet in the School of Psychology on University of Tasmania premises for a period of at least 5 years, after which it will be destroyed.

I agree to participate in this investigation and I understand that I may withdraw at any time without prejudice.

Name of participant:

Signature:

Date:

Statement by researcher:

I have explained this study and the implications of participation in it to this volunteer and I believe that the participant is informed and that he/she understands the implications of participation.

Name of researcher:

Signature:

Private Bag 30 Hobart 96
Tasmania Australia 7001
Telephone (03) 6226 2237
Facsimile (03) 6226 2883

Appendix E

Correlations between Self-Report and Cognitive Variables

Table 2

Correlations between demographic, self-report and cognitive variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
1	-	-.24	.08	-.06	-.26	-.10	-.14	.06	.12	-.15	.16	.20	-.24	-.01	.04	.27	-.09	.06	.26	.14	-.11	-.10	-.17	.05	-.04
2	-	-	-.13	.14	.07	.16	.21	.03	.01	.06	-.01	-.17	-.05	.02	.04	-.05	.04	.07	.26	.14	.09	.09	.19	.02	-.19
3	-	-	-	.17	.09	-.17	.03	.07	-.03	-.22	.28	.33*	.18	.08	-.02	.10	-.04	-.13	-.02	.11	.11	-.12	.10	.18	-.02
4	-	-	-	-	.08	.23	.04	-.06	.02	-.05	.11	.10	.18	.20	.06	.22	.02	.05	.01	.09	.00	-.01	.17	.03	-.02
5	-	-	-	-	-	.01	-.04	0.11	0.13	0.12	.06	.07	-.06	.22	.20	-.14	.14	-.41	.20	.27	.04	.36	-.03	-.04	-.01
6	-	-	-	-	-	-	-.04	-.11	-.13	-.12	.06	.07	-.06	.22	.20	-.14	.12	-.41*	.20	.27	.04	.40	-.03	-.04	-.01
7	-	-	-	-	-	-	-	.71*	.48*	.58*	-.14	-.17	.00	-.16	.05	-.10	.03	-.15	-.12	-.18	-.26*	.11	-.12	-.15	-.16
8	-	-	-	-	-	-	-	-	.47*	.65*	-.10	-.11	-.09	-.23	-.04	-.09	-.06	-.15	-.14	-.22	-.21	-.03	-.24	-.12	-.19
9	-	-	-	-	-	-	-	-	-	.42*	-.11	-.11	-.09	-.18	-.10	.10	-.09	.09	-.16	-.09	-.19	.02	-.00	-.04	-.16
10	-	-	-	-	-	-	-	-	-	-	-.26	-.27	-.06	-.14	-.05	-.11	.08	-.04	-.17	-.31*	-.15	.06	-.02	-.13	.05
11	-	-	-	-	-	-	-	-	-	-	-	.92*	-.06	.05	.08	-.36*	-.08	.03	.11	.16	.01	.14	.13	.07	-.04
12	-	-	-	-	-	-	-	-	-	-	-	-	-.02	.04	.04	.30*	-.05	.07	.10	.18	.10	.08	.15	.07	-.05
13	-	-	-	-	-	-	-	-	-	-	-	-	-	.41*	.39*	.12	.07	-.03	-.11	.09	.17	-.01	.11	.14	.12
14	-	-	-	-	-	-	-	-	-	-	-	-	-	-	.43*	.29*	.09	.16	-.09	.07	.14	-.17	.18	.28	.37*
15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	.02	.13	.12	-.14	-.09	.10	.10	.17	.15	.29*
16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-.12	.10	.13	.20	-.01	-.04	-.11	.22	.20
17	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	.07	.04	.09	.00	.14	.05	.03	.10
18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-.02	-.10	-.06	-.32*	.01	.07	.21
19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	.81*	.30*	-.15	-.02	.07	-.11
20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	.37*	-.14	.17	.08	-.04
21	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-.33*	.25	.23	.19
22	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-.03	-.06	-.00
23	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	.12	.22
24	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	.30*
25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

* $p < .01$

Key to Table 2

- 1 Sex
- 2 Age
- 3 Education
- 4 NART scores converted into IQ scores
- 5 Years since diagnosis
- 6 Weeks since venesection
- 7 Haemochromatosis Symptom Severity score
- 8 Brief Fatigue Inventory score
- 9 Anxiety score (HADS)
- 10 Depression score (HADS)
- 11 Story Recall Immediate recall score
- 12 Story Recall Delayed recall score
- 13 Digit Span score (forwards & backwards combined)
- 14 Letter Number Sequencing score
- 15 PASAT score
- 16 List learning A1-A5 score
- 17 List Learning percentage retained score
- 18 Complex Figure copy score
- 19 Complex Figure Immediate recall score
- 20 Complex Figure Delayed recall score
- 21 Design Learning A1-A5 score
- 22 Design Learning percentage retained score
- 23 Visual Patterns Test score
- 24 Information Processing Task A Speed score
- 25 Information Processing Task A Adjusted Score (adjusted for motor speed)